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(54) Title: CYCLIC PROTEIN TYROSINE KINASE INHIBITORS

(57) Abstract

Novel cyclic compounds and salts thereof, pharmaceutical compositions containing such compounds, and methods of using such compounds in the treatment of protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders.

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# CYCLIC PROTEIN TYROSINE KINASE INHIBITORS

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#### Field of the Invention

The present invention relates to cyclic compounds and salts thereof, to methods of using such compounds in treating protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders, and to pharmaceutical compositions containing such compounds.

#### **Background of the Invention**

Protein tyrosine kinases (PTKs) are enzymes which, in conjuction with ATP as a substrate, phosphorylate tyrosine residues in peptides and proteins. These enzymes are key elements in the regulation of cell signaling including cell proliferation and cell differentiation. PTKs comprise, inter alia, receptor tyrosine kinases (RPTKs), including members of the epidermal growth factor kinase family (e.g., HER1 and HER2), platelet derived growth factor (PDGF), and kinases that play a role in angiogenesis (Tie-2 and KDR); and, in addition, non-receptor tyrosine kinases, including members of the Syk, JAK and Src (e.g. Src, Fyn, Lyn, Lck and Blk) families (see Bolen, J.B., Rowley, R.B., Spana, C., and Tsygankov, A.Y., "The src family of tyrosine protein kinases in hemopoietic signal transduction", FASEB J., 6, 3403-3409 (1992); Ullrich, A. and Schlessinger, J., "Signal transduction by receptors with tyrosine kinase activity", Cell, 61, 203-212 (1990); and Ihle, J.N., "The Janus protein tyrosine kinases in hematopoetic cytokine signaling", Sem. Immunol., 7, 247-254 (1995)).

Enhanced activity of PTKs has been implicated in a variety of malignant and nonmalignant proliferative diseases. In addition, PTKs play a central role in the regulation of cells of the immune system. PTK inhibitors can thus impact a wide variety of oncologic and immunologic disorders. Such disorders may be ameliorated by selective inhibition of a certain receptor or non-receptor PTK, such as Lck, or due to the homology among PTK classes, by inhibition of more than one PTK by an inhibitor.

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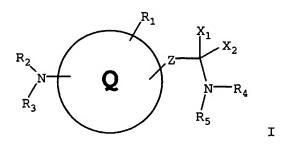
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A PTK of particular interest is Lck which is found in T cells where it is involved in phosphorylating key protein substrates. It is required for productive antigen receptor signaling and cell activation. In the absence of Lck activity, the T cell receptor (TCR) zeta chain is not phosphorylated, the kinase ZAP-70 is not activated, and Ca<sup>2+</sup> mobilization essential for T cell activation does not occur (see Weiss, A. and Littman, D.R., "Signal transduction by lymphocyte antigen receptors", Cell, 76, 263-274 (1994); Iwashima, M., Irving, B.A., van Oers, N.S.C., Chan, A.C., and Weiss, A., "Sequential interactions of the TCR with two distinct cytoplasmic tyrosine kinases", Science, 263, 1136-1139 (1994); and Chan, A.C., Dalton, M., Johnson, R., Kong, G., Wang, T., Thoma, R., and Kurosaki, T., "Activation of ZAP-70 kinase activity by phosphorylation of tyrosine 493 is required for lymphocyte antigen receptor function", EMBO J., 14, 2499-2508 (1995)). Inhibitors of Lck are thus useful in the treatment of T-cell mediated disorders such as chronic diseases with an important T cell component, for example rheumatoid arthritis, multiple sclerosis and lupus, as well as acute diseases where T cells are known to play an essential role, for example acute transplant rejection and delayed-type hypersensitivity (DTH) reactions.

#### Summary of the Invention

The present invention provides cyclic compounds of the following formula I and salts thereof, for use as protein tyrosine kinase inhibitors:

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where

10 Q is:

(1) a 5-membered heteroaryl ring;

- (2) a 6-membered heteroaryl ring; or
- (3) an aryl ring;

optionally substituted with one or more groups R<sub>1</sub>;

15 Z is:

- (1) a single bond;
- (2)  $-R_{15}C=CH-$ ; or
- (3)  $-(CH_2)_m$ -, where m is 1 to 2;
- 20  $X_1$  and  $X_2$  are each hydrogen, or together form =0 or =S;  $R_1$  is:
  - (1) hydrogen or  $R_6$ , where  $R_6$  is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or

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more (preferably, one or two) groups  $Z_3$ ;

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(2)
                         -OH or -OR<sub>s</sub>;
                         -SH or -SR<sub>6</sub>;
              (3)
                         -C(O)<sub>2</sub>H, -C(O)<sub>q</sub>R<sub>6</sub>, or -O-C(O)<sub>q</sub>R<sub>6</sub>, where q is 1 or 2;
              (4)
              (5)
                         -SO_3H or -S(O)_0R_6;
  5
                         halo;
              (6)
              (7)
                         cyano;
              (8)
                         nitro;
              (9)
                         -Z_4-NR_7R_8;
              (10)
                         -Z_4-N(R_9)-Z_5-NR_{10}R_{11};
                         -Z_4-N(R_{12})-Z_5-R_6;
10
              (11)
                         -P(O)(OR_e)_{o};
              (12)
        R_2 and R_3 are each independently:
                        hydrogen or R<sub>6</sub>;
              (1)
                        -Z_4-R_6; or
              (2)
15
                        -Z_{13}-NR_{7}R_{8};
              (3)
        R_4 and R_5:
              (1)
                        are each independently hydrogen or R<sub>s</sub>;
                        -Z_4-N(R_0)-Z_5-NR_{10}R_{11};
              (2)
                        -N(R_9)Z_4R_6; or
              (3)
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              (4)
                        together with the nitrogen atom to which they are attached
                                complete a 3- to 8-membered saturated or unsaturated
                                heterocyclic ring which is unsubstituted or substituted
                                with Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>, which heterocyclic ring may
                                optionally have fused to it a benzene ring itself
25
                                unsubstituted or substituted with Z_1, Z_2 and Z_3;
       R_7, R_8, R_9, R_{10}, R_{11} and R_{12}:
                        are each independently hydrogen or Re;
             (1)
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 $R_7$  and  $R_8$  may together be alkylene, alkenylene or heteroalkyl, completing a 3- to 8-membered saturated or unsaturated ring with the nitrogen atom to which

they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ; or

(3) any two of  $R_9$ ,  $R_{10}$  and  $R_{11}$  may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ;

R<sub>13</sub> is:

- (1) cyano;
- 10 (2) nitro;
  - $(3) -NH_2;$ 
    - (4) -NHOalkyl;
    - (5) -OH;
    - (6) -NHOaryl;
- 15 (7) -NHCOOalkyl;
  - (8) -NHCOOaryl;
  - (9) -NHSO<sub>2</sub>alkyl;
  - (10) -NHSO<sub>2</sub>aryl;
  - (11) aryl;
- 20 (12) heteroaryl;
  - (13) -Oalkyl; or
  - (14) -Oaryl;

 $R_{14}$  is:

- (1)  $-NO_2$ ;
- 25 (2) -COOalkyl; or
  - (3) -COOaryl;

R<sub>15</sub> is:

- (1) hydrogen;
- (2) alkyl;
- 30 (3) aryl;
  - (4) arylalkyl; or

(5) cycloalkyl;

 $Z_{\scriptscriptstyle 1},\,Z_{\scriptscriptstyle 2}$  and  $Z_{\scriptscriptstyle 3}$  are each independently:

- (1) hydrogen or Z<sub>6</sub>, where Z<sub>6</sub> is (i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenyl, aralkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is substituted by one or more of the following groups (2) to (16) of the definition of Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>;
- (2) -OH or -O $Z_s$ ;
  - (3) -SH or -S $Z_{\epsilon}$ ;
  - (4)  $-C(O)_{o}H$ ,  $-C(O)_{o}Z_{6}$ , or  $-O-C(O)_{o}Z_{6}$ ;
  - (5)  $-SO_3H$ ,  $-S(O)_qZ_6$ ; or  $S(O)_qN(Z_9)Z_6$ ;
- 15 (6) halo;

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- (7) cyano;
- (8) nitro;
- (9)  $-Z_1-NZ_7Z_9$ ;
- (10)  $-Z_4-N(Z_9)-Z_5-NZ_7Z_8$ ;
- 20 (11)  $-Z_4-N(Z_{10})-Z_5-Z_5$ ;
  - (12)  $-Z_4-N(Z_{10})-Z_5-H;$
  - (13) oxo;
  - (14)  $-O-C(O)-Z_{\epsilon}$ ;
- (15) any two of Z<sub>1</sub>, Z<sub>2</sub>, and Z<sub>3</sub> may together be alkylene or
  25 alkenylene completing a 3- to 8-membered saturated
  or unsaturated ring together with the atoms to which
  they are attached; or
- (16) any two of Z<sub>1</sub>, Z<sub>2</sub>, and Z<sub>3</sub> may together be -O-(CH<sub>2</sub>)<sub>r</sub>-O- ,where
  r is 1 to 5, completing a 4- to 8-membered saturated or
  unsaturated ring together with the atoms to which
  they are attached;

 $Z_4$  and  $Z_5$  are each independently:

- (1) a single bond;
- (2)  $-Z_{11}-S(O)_{a}-Z_{12}-;$
- (3)  $-Z_{11}$ -C(O)- $Z_{12}$ -;
- 5 (4)  $-Z_{11}$ -C(S)- $Z_{12}$ -;
  - (5)  $-Z_{1},-O-Z_{2}$ ;
  - (6)  $-Z_{11}-S-Z_{12}-;$
  - (7)  $-Z_{11}$ -O-C(O)- $Z_{12}$ -; or
  - (8)  $-Z_{11}$ -C(O)-O- $Z_{12}$ -;
- 10  $Z_7$ ,  $Z_8$ ,  $Z_9$  and  $Z_{10}$ :

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- (1) are each independently hydrogen or  $Z_6$ ;
- (2)  $Z_7$  and  $Z_8$ , or  $Z_6$  and  $Z_{10}$ , may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ; or
- (3) Z<sub>7</sub> or Z<sub>8</sub>, together with Z<sub>9</sub>, may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>;

 $Z_{11}$  and  $Z_{12}$  are each independently:

- (1) a single bond;
- (2) alkylene;
- 25 (3) alkenylene; or
  - (4) alkynylene; and

 $Z_{13}$  is:

- (1) a single bond;
- (2)  $-Z_{11}-S(O)_{0}-Z_{12}-;$
- 30 (3)  $-Z_{11}-C(O)-Z_{12}-$ ;
  - (4)  $-Z_{11}$ -C(S)- $Z_{12}$ -;

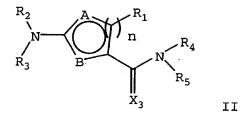
- (5)  $-Z_{11}-O-Z_{12}-;$
- (6)  $-Z_{11}-S-Z_{12}-;$
- (7)  $-Z_{11}$ -O-C(O)- $Z_{12}$ -;
- (8)  $-Z_{11}-C(O)-O-Z_{12}-;$

5 (9)  $-C(NR_{13})$ -;

- (10) -C(CHR<sub>14</sub>)-; or
- (11)  $-C(C(R_{14})_2)$ -.

Compounds within formula I include compounds of the following formula II and salts thereof:

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where

n is 1 or 2

15 A is selected from carbon and nitrogen;

B is selected from nitrogen, oxygen and sulfur;

 $X_3$  is oxygen or sulfur; and

 $R_{\mbox{\tiny 1}},\,R_{\mbox{\tiny 2}},\,R_{\mbox{\tiny 3}},\,R_{\mbox{\tiny 4}}$  and  $R_{\mbox{\tiny 5}}$  are as described above.

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# **Detailed Description of the Invention**

The following are definitions of terms used in this specification.

The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated.

The terms "alk" or "alkyl" refer to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon

atoms. The expression "lower alkyl" refers to alkyl groups of 1 to 4 carbon atoms.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one double bond. Where an alkenyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a double bond.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one triple bond. Where an alkynyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a triple bond.

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The term "alkylene" refers to a straight chain bridge of 1 to 5 carbon atoms connected by single bonds (e.g.,  $-(CH_2)_{X^-}$  wherein x is 1 to 5), which may be substituted with 1 to 3 lower alkyl groups.

The term "alkenylene" refers to a straight chain bridge of 2 to 5 carbon atoms having one or two double bonds that is connected by single bonds and may be substituted with 1 to 3 lower alkyl groups. Exemplary alkenylene groups are -CH=CH-CH=CH-, -CH2-CH=CH-,

20 -CH2-CH=CH-CH2-, -C(CH3)2CH=CH- and -CH(C2H5)-CH=CH-.

The term "alkynylene" refers to a straight chain bridge of 2 to 5 carbon atoms that has a triple bond therein, is connected by single bonds, and may be substituted with 1 to 3 lower alkyl groups. Exemplary alkynylene groups are -C= C-, -CH<sub>2</sub>-C= C-, -CH(CH<sub>3</sub>)-C= C- and -C= C-CH(C<sub>2</sub>H<sub>5</sub>)CH<sub>2</sub>-.

The terms "ar" or "aryl" refer to aromatic cyclic groups (for example 6 membered monocyclic, 10 membered bicyclic or 14 membered tricyclic ring systems) which contain 6 to 14 carbon atoms. Exemplary aryl groups include phenyl, naphthyl, biphenyl and anthracene.

The terms "cycloalkyl" and "cycloalkenyl" refer to cyclic hydrocarbon groups of 3 to 12 carbon atoms.

The terms "halogen" and "halo" refer to fluorine, chlorine, bromine and iodine.

The term "unsaturated ring" includes partially unsaturated and aromatic rings.

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The terms "heterocycle", "heterocyclic" or "heterocyclo" refer to fully saturated or unsaturated, including aromatic (i.e. "heteroaryl") cyclic groups, for example, 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring systems, which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolyl, imidazolyl, imidazolyl, imidazolyl, imidazolyl, isoxazolyl, thiazolyl, thiazolyl, thiazolyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, triazolyl, triazinyl, and the like.

Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl, benzoxazolyl, benzodioxolyl, benzothienyl, quinuclidinyl, quinolinyl, tetra-hydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or

furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), tetrahydroquinolinyl and the like.

Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

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The term "heteroaryl" refers to aromatic heterocyclic groups.

Exemplary heteroaryl groups include pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furyl, thienyl, oxadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, triazinyl, and the like.

Where q is 1 or 2, "-C(O)<sub>q</sub>H" denotes -C(O)-H or -C(O)-OH; "-C(O)<sub>q</sub>R<sub>6</sub>" or "-C(O)<sub>q</sub>Z<sub>6</sub>" denote, respectively, -C(O)-R<sub>6</sub> or -C(O)-OR<sub>6</sub>, or -C(O)-Z<sub>6</sub> or -C(O)-OZ<sub>6</sub>; "-O-C(O)<sub>q</sub>R<sub>6</sub>" or "-O-C(O)<sub>q</sub>Z<sub>6</sub>" denote, respectively, -O-C(O)-R<sub>6</sub> or -O-C(O)-OR<sub>6</sub>, or -O-C(O)-Z<sub>6</sub> or -O-C(O)-OZ<sub>6</sub>; and "-S(O)<sub>q</sub>R<sub>6</sub>" or "-S(O)<sub>q</sub>Z<sub>6</sub>" denote, respectively, -SO-R<sub>6</sub> or -SO<sub>2</sub>-R<sub>6</sub>, or -SO-Z<sub>6</sub> or -SO<sub>2</sub>-Z<sub>6</sub>.

Compounds of the formula I may in some cases form salts which are also within the scope of this invention. Reference to a compound of the formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. Zwitterions (internal or inner salts) are included within the term "salt(s)" as used herein (and may be formed, for example, where the R substituents comprise an acid moiety such as a carboxyl group). Also included herein are quaternary ammonium salts such as alkylammonium salts. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are useful, for example, in isolation or purification steps which may be employed during preparation. Salts of the compounds of the formula I may be formed, for example, by reacting a compound I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates, undecanoates, and the like.

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Exemplary basic salts (formed, for example, where the R substituents comprise an acidic moiety such as a carboxyl group) include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines, N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. The basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound which, upon administration to a subject, undergoes chemical

conversion by metabolic or chemical processes to yield a compound of the formula I, or a salt and/or solvate thereof. Solvates of the compounds of formula I are preferably hydrates.

All stereoisomers of the present compounds, such as those which may exist due to asymmetric carbons on the R substituents of the compound of the formula I, including enantiomeric and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations.

Throughout the specification, groups and substituents thereof are chosen to provide stable moieties and compounds.

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#### Preferred Compounds

Preferred compounds of the present invention are compounds of the formula I, and salts thereof, wherein Q is thiazole and wherein one or more, and especially all, of Z,  $X_1$ ,  $X_2$   $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ , and  $R_5$  are selected from the following definitions:

Z is a single bond;

R<sub>1</sub> is selected from hydrogen, halo, alkyl, aryl, alkoxy, alkoxycarbonyl, or aryloxycarbonyl and is more preferably hydrogen;

 $X_1$  and  $X_2$  together form =0 or =S and more preferably form =0;

R, is hydrogen;

 $R_3$  is selected from  $-Z_4-R_6$  or  $-Z_{13}-NR_7R_8$  and is more preferably  $-Z_4-R_6$  wherein  $Z_4$  is a single bond and  $R_6$  is aryl or heteroaryl which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or more (preferably, one or two) groups  $Z_3$ ;

30 R, is hydrogen; and

 $R_5$  is selected from aryl groups or heteroaryl groups which are substituted with  $Z_1$ ,  $Z_2$  and one or more (such as one or two) groups  $Z_3$ .

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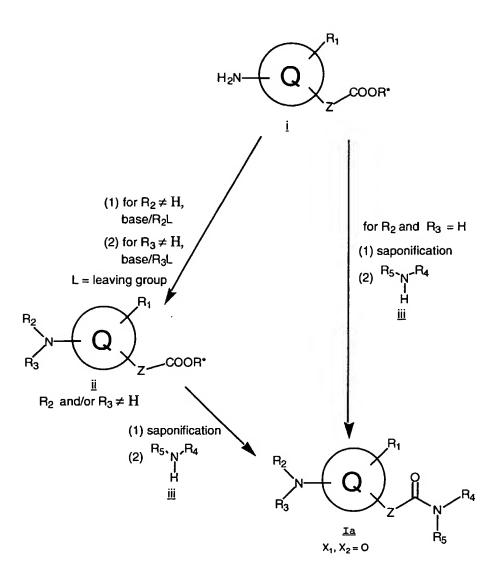
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#### Methods of Preparation

The compounds of the formula I may be prepared by methods such as those illustrated in the following Schemes A through E and I through XI. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. All documents cited are incorporated herein by reference in their entirety. Starting materials are commercially available or readily prepared by one of ordinary skill in the art. Constituents of compounds are as defined elsewhere in the specification or as specifically defined in a scheme.

The methods described herein may be carried out with starting materials and/or reagents in solution or alternatively, where appropriate, 15 with one or more starting materials or reagents bound to a solid support (see (1) Thompson, L. A., Ellman, J. A., Chemical Reviews, 96, 555-600 (1996); (2) Terrett, N. K., Gardner, M., Gordon, D. W., Kobylecki, R. J., Steele, J., Tetrahedron, 51, 8135-8173 (1995); (3) Gallop, M. A., Barrett, R. W., Dower, W. J., Fodor, S. P. A., Gordon, E. M., Journal of Medicinal 20 Chemistry, 37, 1233-1251 (1994); (4) Gordon, E. M., Barrett, R. W., Dower, W. J., Fodor, S. P. A., Gallop, M. A., Journal of Medicinal Chemistry, 37, 1385-1401 (1994); (5) Balkenhohl, F., von dem Bussche-Hünnefeld, Lansky, A., Zechel, C., Angewandte Chemie International Edition in English, 35, 2288-2337 (1996); (6) Balkenhohl, F., von dem Bussche-25 Hünnefeld, Lansky, A., Zechel, C., Angewandte Chemie, 108, 2436-2487 (1996); and (7) Sofia, M. J., Drugs Discovery Today, 1, 27-34 (1996)).

# Scheme A



Scheme A illustrates a general method for forming compound Ia, which is a compound of the formula I where  $X_1$  and  $X_2$  together form =0. As shown in Scheme A, compound Ia where  $R_2$  and  $R_3$  are hydrogen may be formed by saponification of  $\underline{\mathbf{i}}$ ,  $(R^*$  is a carboxyl protecting group such as alkyl or arylalkyl) followed by reaction with amine  $\underline{\mathbf{iii}}$  by methods known in the art. Alternatively  $\underline{\mathbf{i}}$  may be reacted with  $R_2L$ , where L is a leaving group such as halogen (for example, in equimolar portions), optionally followed by reaction with  $R_3L$  (for example, in equimolar portions) to form  $\underline{\mathbf{ii}}$ . Also alternatively,  $\underline{\mathbf{i}}$  may be subjected to reductive amination using the appropriate aldehyde or ketone to form  $\underline{\mathbf{ii}}$ . The compound  $\underline{\mathbf{ii}}$  may then be saponified and reacted with amine  $\underline{\mathbf{iii}}$ , under conditions known to those skilled in the art, to form Ia where  $R_2$  and/or  $R_3$  are other than hydrogen.

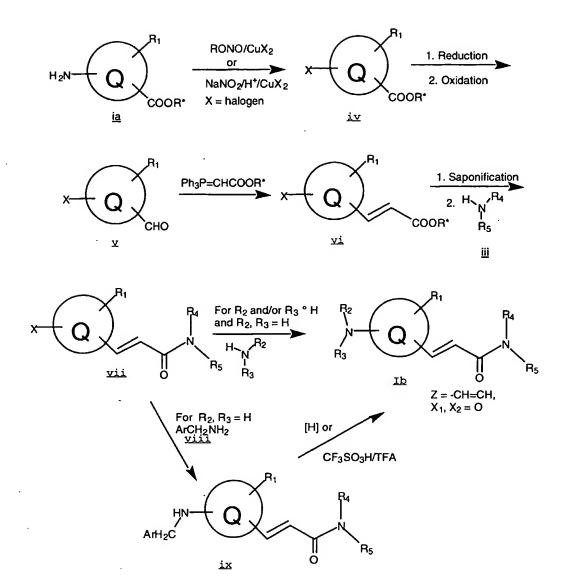
Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

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# Scheme B



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Scheme B illustrates a general method for forming compound Ib, which is a compound of formula I where Z is -CH=CH- and  $X_1$  and  $X_2$ together form =O. As shown in Scheme B, a 2-halo-compound vi can be prepared by reacting an appropriately substituted 2-amino-compound ia with copper (ii) halide and an alkyl nitrite such as tert-butyl nitrite in an aprotic solvent such as acetonitrile to form 2-halo-compound  $\underline{iv}$  (see J. Het.Chem. 22, 1621 (1985)). Compound iv can be reduced with a reducing agent such as sodium borohydride in ethanol or aqueous tetrahydrofuran to form an alcohol, which can be oxidized with an oxidizing agent such as pyridinium chlorochromate or pyridinium dichromate to form aldehyde v. Compound  $\underline{\mathbf{v}}$  can be reacted with an alkyl(triphenylphosphorylidene) acetate to form carboxylate vi. Compound vi can be saponified and then reacted with an amine iii by methods known to those skilled in the art to form vii. Compound vii can be reacted with an amine R2R3NH to form Ib where Z is -CH=CH- and  $X_1$ ,  $X_2$  together form =0. Alternatively, compounds of formula Ib where R2 and R3 are H, can be formed by reacting compound vii with an appropriately substituted benzyl amine such as 4methoxybenzyl amine to form compound ix, which can be hydrogenolyzed or treated with an acid such as trifluoromethanesulfonic acid and trifluoroacetic acid in the presence of anisole to form Ib where  $\boldsymbol{R}_{\!\scriptscriptstyle 2}$  and  $\boldsymbol{R}_{\!\scriptscriptstyle 3}$ are hydrogen.

Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

# Scheme C

$$\begin{array}{c} 1. \text{ Saponification} \\ 2. R_{15}\text{Li} \\ \\ R_{15} \\ \\ \end{array} \begin{array}{c} 1. \text{ Ph}_{3}\text{P=CHCOOR'} \\ \\ R_{15} \\ \\ \end{array} \begin{array}{c} 1. \text{ Ph}_{3}\text{P=CHCOOR'} \\ \\ \hline \\ 2. \text{ Deprotection} \\ \\ \end{array} \begin{array}{c} 1. \text{ Ph}_{3}\text{P=CHCOOR'} \\ \\ \hline \\ 2. \text{ Deprotection} \\ \end{array} \\ \begin{array}{c} 1. \text{ Saponification} \\ \\ \hline \\ 2. \text{ For } R_{2}, R_{3} = H \\ \\ \hline \\ 1. \text{ saponification} \\ \\ \hline \\ 2. \text{ For } R_{3} \circ H \\ \\ \hline \\ 1. \text{ Saponification} \\ \\ \hline \\ 1. \text{ Saponification} \\ \\ \hline \\ 2. \text{ For } R_{3} \circ H \\ \\ \hline \\ R_{2} \text{ and/or } R_{3} \circ H \\ \end{array} \\ \begin{array}{c} 1. \text{ Ph}_{3}\text{P=CHCOOR'} \\ \hline \\ 2. \text{ Deprotection} \\ \hline \\ 2. \text{ Ph}_{3}\text{P=CHCOOR'} \\ \hline \\ 2. \text{ Deprotection} \\ \hline \\ 2. \text{ For } R_{3} \circ H \\ \hline \\ 1. \text{ Saponification} \\ \hline \\ 2. \text{ For } R_{3} \circ H \\ \hline \\ R_{15} \\ \hline \\ R_{2} \text{ and/or } R_{3} \circ H \\ \end{array}$$

Scheme C illustrates a general method for forming compound Ic, which is a compound of formula I where Z is -R<sub>15</sub>C=CH- and X<sub>1</sub> and X<sub>2</sub> together form =O. As shown in Scheme C, a 2-amino-compound <u>ia</u> can be reacted with a chloroformate or dicarbonate to form <u>x</u>, which can be saponified and treated with an organolithium reagent to form compound <u>xi</u>. Compound <u>xi</u> may be reacted with an alkyl(triphenylphosphorylidene)acetate, followed by deprotection of the carbamate protecting group to form <u>xii</u>. Alternatively, compound Ic where R<sub>2</sub> and R<sub>3</sub> are hydrogen may be formed by saponification of <u>xii</u> followed by reaction with an amine R<sub>4</sub>R<sub>5</sub>NH by methods known to those skilled in the art. Alternatively, compound xii may be reacted with R<sub>2</sub>L where L is a leaving group such as halogen (for example, in equimolar portions), optionally followed by reaction with R<sub>3</sub>L

(for example, in equimolar portions) to form  $\underline{xiii}$ , which may be saponified and reacted with an amine  $R_4R_5NH$  by methods known to those skilled in the art to form Ia where  $R_2$  and/or  $R_3$  are other than hydrogen.

Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

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#### Scheme D

Scheme D illustrates a general method for forming compound Id, which is a compound of the formula I where X<sub>1</sub> and X<sub>2</sub> together form =S. The compounds of the formula Ia obtained in Scheme A may be converted into the corresponding thioamide Id using a reagent such as Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (see *Bull. Soc. Chim. Belg.*, 87, 223 (1978)).

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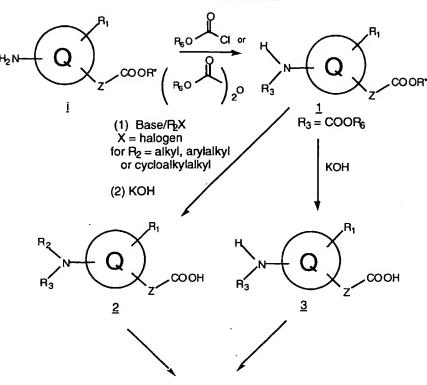
Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

# Scheme E

Scheme E illustrates a general method for forming compound Ie, which is a compound of the formula I where X<sub>1</sub> and X<sub>2</sub> are each hydrogen. As shown in Scheme E, the compound of the formula Id obtained in Scheme D may be converted into the corresponding amine Ie by reduction, for example, by reaction with Raney nickel.

Methods for preparing preferred substituents on the compounds I are illustrated in the following Schemes I to XI.

# Scheme I



(A) peptide bond synthesis, i.e.,

(B) synthesis via acid chloride, i.e.,
(1) thionyl chloride or oxalyl chloride

$$(2) \xrightarrow{R_5} N \xrightarrow{R_4}$$

$$\downarrow \qquad \qquad \downarrow \qquad \qquad$$

 $R_3 = COOR_6$  $X_1, X_2 = O$ 

starting from ≥ R<sub>2</sub> = alkyl, arylalkyl or cycloalkylalkyl starting from 3: R<sub>2</sub> = H

As shown in Scheme I, carboxylate  $\underline{i}$  can be reacted with a chloroformate or dicarbonate to form  $\underline{1}$ . Compound  $\underline{1}$  can be treated with a base such as sodium hydride, sodium/potassium hexamethyldisilazide, or lithium diisopropylamide (LDA), and an alkylating agent  $R_2X$  where X is halogen and  $R_2$  is preferably alkyl, arylalkyl, or cycloalkylalkyl, and then saponified with an aqueous base such as potassium hydroxide to give  $\underline{2}$ . Alternatively,  $\underline{1}$  can the subjected to reductive amination using the appropriate aldehyde or ketone and saponified with an aqueous base such as potassium hydroxide to give  $\underline{2}$ . Compound  $\underline{1}$  may, alternatively, be simply saponified with an aqueous base such as potassium hydroxide to give  $\underline{3}$  where  $R_2$  is hydrogen.

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Acid  $\underline{2}$  may be reacted with an amine  $\underline{iii}$  using reaction conditions well known in the art for peptide bond synthesis (see, for example, Bodanszky and Bodanszky, The Practice of Peptide Chemistry, Springer-Verlag, 1984; Bodanszky, Principles of Peptide Synthesis, Springer-Verlag, 1984) to give the compound Id which a compound of the formula I where  $X_1$  and  $X_2$  together form =0,  $R_3$  is  $COOR_6$ , and, since  $\underline{2}$  is the starting material,  $R_2$  is preferably alkyl, arylalkyl or cycloalkylalkyl. For example, reagents which activate the carboxyl group of  $\underline{2}$  for reaction with the amine  $\underline{iv}$  include bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP chloride), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent), [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium] hexafluorophosphate (HATU), and carbodiimides such as dicyclohexylcarbodiimide (DCC) or 3-ethyl-3'-

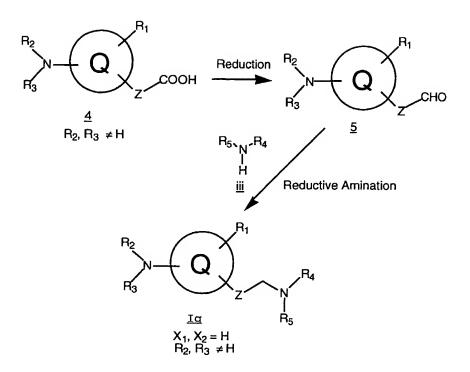
(dimethylamino)propylcarbodiimide (EDCI) either alone or in combination with a hydroxybenzotriazole. Alternatively, the activated ester intermediate can be isolated and then treated with the appropriate amine iv in a nonprotic solvent such as tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base, for example, an organic base such as sodium/potassium hexamethyldisilazide, triethylamine, diisopropylethylamine or 1,8-diazabicyclo[5.4.0]undec-7-

ene (DBU), or an inorganic base such as sodium, potassium or cesium carbonate or sodium or potassium hydride. Alternatively, the acid halide of  $\underline{2}$  may be prepared, for example, by reaction with thionyl chloride or oxalyl chloride, followed by subsequent reaction with amine  $\underline{iii}$  to provide compound If, which is a compound of the formula I where  $R_3$  is  $COOR_6$ ,  $X_1$  and  $X_2$  together form =0, and  $R_2$  is alkyl, arylalkyl or chycloalkylalkyl.

Similar reactions as employed above for the conversion of  $\underline{2}$  to If may be used to convert  $\underline{3}$  to If where  $R_3$  is  $COOR_6$ ,  $X_1$  and  $X_2$  together form =0, and  $R_2$  is hydrogen.

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# Scheme II



As shown in Scheme II, acid  $\underline{4}$  where  $R_2$  and  $R_3$  are not hydrogen and are selected such that the nitrogen to which they are attached is non-basic, is reduced to the aldehyde  $\underline{5}$  by methods well know in the art (see March, Advanced Organic Chemistry, Wiley, 1985). For example, the acid  $\underline{4}$  may be converted to its corresponding ester followed by reduction with diisobutylaluminum hydride. Alternatively, the acid  $\underline{4}$  may be reduced to the corresponding primary alcohol, for example, by treatment with borane/THF, LiAlH<sub>4</sub>, or via reduction of a mixed anhydride, followed by subsequent oxidation to the aldehyde  $\underline{5}$  using Cr(VI) (e.g., pyridinium chlorochromate, "PCC") or under Swern or Moffatt conditions (e.g., (COCl)/dimethylsulfoxide). The starting acid  $\underline{4}$  may be obtained, for example, by saponification of  $\underline{ii}$ .

Reductive amination (see Hudlicky, Reductions in Organic Chemistry, Wiley, 1984) of aldehyde  $\underline{\mathbf{5}}$  with amine  $\underline{\mathbf{iii}}$  in the presence of a reducing agent such as NaBH<sub>3</sub>CN, NaBH(OAc)<sub>3</sub> (Ac = acetyl) or hydrogen and a palladium catalyst produces the amine compound Ig, which is a compound of the formula I where  $X_1$  and  $X_2$  are each hydrogen and  $R_2$  and  $R_3$  are each not hydrogen.

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#### Scheme III

$$R_2$$
 $R_3$ 
 $R_4$ 
 $R_4$ 
 $R_5$ 
 $R_5$ 
 $R_4$ 
 $R_5$ 
 $R_5$ 
 $R_5$ 
 $R_5$ 
 $R_4$ 
 $R_5$ 
 $R_5$ 
 $R_5$ 

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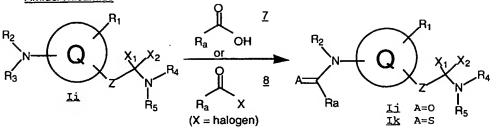
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As shown in Scheme III, reduction of the acid  $\underline{4}$  to a primary alcohol (for example, by treatment with borane/tetrahydrofuran, LiAlH<sub>4</sub>, or via reduction of a mixed anhydride), followed by conversion by methods well known in the art (see March, Advanced Organic Chemistry, Wiley, 1985), provides  $\underline{6}$  which contains a leaving group such as a halide, tosylate (OTs), mesylate (OMs) or triflate (OTf). The groups  $R_2$  and  $R_3$  are selected such that the resulting nitrogen to which they are attached is non-basic. Compound  $\underline{6}$  can then be converted into compound Ih, which is a compound of the formula I where  $X_1$  and  $X_2$  are each hydrogen and  $R_2$  and  $R_3$  are each not hydrogen, by a displacement reaction with amine  $\underline{iii}$ , preferably where amine  $\underline{iii}$  is used in excess.

# Scheme IV

 $R_2$  = any group as defined  $R_3$  = acyl or thioacyl

#### Amide/Thioamide



# Carbamate $\begin{array}{c|c} Carbamate & 9 \\ \hline & X_1 & X_2 \\ \hline & X_1 & X_2 \\ \hline & R_6 & OrCl \\ \hline & 10 & 10 \\ \hline \end{array}$

# $Q = Q = Q = X_1 \times X_2 \times X_1 \times X_2 \times X_2 \times X_2 \times X_1 \times X_2 \times X_1 \times X_2 \times X_2 \times X_1 \times X_2 \times X_2 \times X_2 \times X_1 \times X_2 \times X_2$

#### Urea/Thiourea

 $[X_1,X_2\neq H]$ 

Scheme IV illustrates methods which may be used for the preparation of compounds Ij, Ik, Il, Im and In. Ij, Ik, Il, Im and In are compounds of the formula I where  $R_2$  is any group as defined,  $R_3$  is an acyl or thioacyl group,  $X_1$  and  $X_2$  are not hydrogen, and  $R_1$  is not a primary or secondary amine. Ij, Ik, Il, Im and In have other particular substituents which are specified in this Scheme and below. The starting compound Ii can be prepared by suitable methods described in Schemes A and D.

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Amide Ij can be prepared by treatment of amine compound Ii with a carboxylic acid  $\underline{7}$  in the presence of reagents which activate the carboxyl group for reaction as described above, for example BOP reagent, HATU, and carbodiimides such as DCC or EDCI either alone or in combination with a hydroxybenztriazole. Alternatively, the acid halide  $\underline{8}$  may be reacted with amine compound Ii in the presence of an acid scavenger such as diisopropylethylamine. The corresponding thioamide Ik can be prepared by the treatment of amide Ii (where  $X_1, X_2 \neq 0$ ) with Lawesson's reagent as described above.

Carbamate II can be prepared by treatment of amine compound Ii with a chloroformate  $\underline{9}$  or dicarbonate  $\underline{10}$  in the presence of an acid scavenger such as diisopropylethylamine.

The urea Im may be prepared by treatment of amine compound Ii with either: 1) a chloroformate  $\underline{9}$ , such as phenylchloroformate, followed by reaction with an amine  $\underline{11}$ ; 2) a carbamoyl chloride  $\underline{12}$  in the presence of an acid scavenger such as diisopropylethylamine; or 3) reaction with an isocyanate  $\underline{13a}$  (where  $R_c$  in Im = H). The corresponding thiourea In may be prepared by treatment of amine compound Ii with a thioisocyanate  $\underline{13b}$ .

 $R_a$  is selected from those groups included in the definition of  $R_6$  such that the group -C(=A)- $R_a$  is an acyl or thioacyl group within the definition of  $R_3$ .  $R_b$  and  $R_c$  are selected from those groups included in the definitions of  $R_7$  and  $R_8$ , such that the group -C(=A)-N( $R_b$ )( $R_c$ ) is an acyl or thioacyl group within the definition of  $R_3$ .

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# Scheme V

 $R_2$  = any group as defined other than acyl  $R_3$  = alkyl, cycloalkyla, cycloalkylalkyl, cycloalkylalkyl, aralkyl or saturated heterocycle

Scheme V illustrates a method which can be used for the preparation of Ip, which is a compound of the formula I where  $R_2$  is any group as defined other than acyl, and which is selected such that the nitrogen to which it is attached is basic,  $R_3$  is alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, or saturated heterocycle, and  $X_1$  and  $X_2$  are not hydrogen. The starting compounds Io and Iq can be prepared by suitable methods described in Schemes A and D.

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As shown in Scheme V, amine compound Io is reacted with an aldehyde or ketone  $\underline{14}$  under reductive amination conditions described above to give the amine Ip. Compound Ip may also be prepared by treatment of an amine compound Iq, where  $R_2$  and  $R_3$  are hydrogen, with t-butyl nitrite or sodium nitrite in the presence of a copper (II) halide to give the halo-substituted compound  $\underline{15}$ , followed by displacement with amine  $\underline{16}$  in the presence of a base such as sodium or potassium hydride or the like (see Lee et al., *J. Heterocyclic Chemistry*, 22, 1621 (1985)).

 $R_d$  and  $R_e$  are independently selected from hydrogen, alkyl, aryl, cycloalkyl or cycloalkenyl, or together are alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring, such that the group -CH( $R_d$ )( $R_e$ ) is a group within the definition of  $R_a$ .

#### Scheme VI

 $R_2$  = any group as defined other than acyl  $R_3$  = aryl, heteroaryl

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As shown in Scheme VI, when R<sub>2</sub> is any group as defined other than acyl, and is selected such that the nitrogen to which it is attached is basic, R<sub>3</sub> is aryl or heteroaryl, and X<sub>1</sub> and X<sub>2</sub> are not hydrogen, amine compound Ir may be reacted with a halophenyl or haloheteroaromatic group <u>17</u> in the presence of a palladium (0) catalyst (see J. Am. Chem. Soc., 118, 7215 (1996)) to give amine Is, which is a compound of the formula I having the particular substituents described in this Scheme. The starting compound Ir can be prepared by suitable methods described in Schemes A and D.

#### Scheme VII

$$R_2$$
 = any group as defined  $R_3$  = heteroaryl  $R_1$   $R_2$   $R_3$  = heteroaryl  $R_4$   $R_5$   $R_5$   $R_5$   $R_6$   $R_7$   $R_8$   $R_8$ 

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As shown in Scheme VII, when R<sub>2</sub> is any group as defined and R<sub>3</sub> is a heteroaromatic group, amine compound It may be reacted, in the presence of a base if needed, with a 2-halosubstituted heteroaromatic compound 17 where Q<sub>1</sub>, together with atoms to which is is bonded, forms a 5- or 6-membered monocyclic or 10- to 12-membered bicyclic heteroaromatic group (such as forming 2-chloropyridine or 2-chloropyrimidine) to give the amine Iu, where Iu is a compound of the formula I having the particular substituents described in this Scheme.

The starting compound It can be prepared by suitable methods described in Schemes A and D.

#### Scheme VIII

As shown in Scheme VIII, thiourea compound In (where X<sub>1</sub> and X<sub>2</sub> are not hydrogen) may be reacted with the appropriate amine in the presence of bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP chloride) benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP-reagent), [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate (HATU) and carbodiimide, such as dicyclohexyl carbodiimide (DCC) or 3-ethyl-3'-(dimethylamino)propyl carbodiimide (EDCI) or diisopropyl carbodiimide (DIC) in the presence of an organic base such as triethylamine, diisopropylethylamine or dimethylaminopyridine in solvents such as dimethylformamide, dichloromethane or tetrahydrofuran to form compound Iv, which is a compound of the formula I having the particular substituents described in this Scheme.

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Alternatively, Compound In can be reacted with the appropriate amine in the presence of a mercury (II) salt such as mercuric chloride, or by other methods known in the literature, to form Iv.

#### Scheme IX

PhO OPh

$$R_2$$
 $R_3$ 
 $R_4$ 
 $R_5$ 
 $R_4$ 
 $R_5$ 
 $R_5$ 
 $R_5$ 
 $R_5$ 
 $R_5$ 
 $R_7$ 
 $R_8$ 
 $R_7$ 
 $R_8$ 
 $R_7$ 
 $R_8$ 
 $R_8$ 

As shown in Scheme IX, amine Ir (where X<sub>1</sub> and X<sub>2</sub> are not hydrogen)

5 can be reacted with diphenylcyanocarbonimidate either alone or in the presence of a base such as sodium hydride, sodium hexamethyldisilazide or dimethylaminopyridine in acetonitrile, tetrahydrofuran, or dimethylformamide at room temperature or elevated temperature to form intermediate compound Iw. Compound Iw can be reacted with an amine

10 R<sub>7</sub>R<sub>8</sub>NH to form compound Iv, which is a compound of the formula I having the particular substituents described in this Scheme.

#### Scheme X

MeS SMe or MeS SMe or 
$$R_{14}$$
  $R_{14}$   $R_{15}$   $R_{15}$   $R_{14}$   $R_{14}$   $R_{14}$   $R_{15}$   $R_{15}$   $R_{14}$   $R_{14}$   $R_{15}$   $R_{15}$ 

As shown in Scheme X, compound Ir (where  $X_1$  and  $X_2$  are not hydrogen) can be reacted with <u>18</u> or <u>19</u> either alone or in the presence of a base such as sodium hydride, sodium hexamethyl disilazide or dimethylaminopyridine in dimethyl formamide or tetrahydrofuran at room temperature or at higher temperature to form compounds Ix or Iy respectively, which can be reacted with an amine  $R_7R_8NH$  at room temperature or elevated temperature to form compounds Iz or Iz\*

Ιz

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respectively. Compound Iz is a compound of the formula I having the particular substituents described in this Scheme. Compound Iz\* is a compound of the formula I having the particular substituents described in this Scheme.

#### Scheme XI

R<sub>2</sub> = aryl, heteroaryl, bicyclic-heteroaryl R<sub>3</sub> = H, alkyl, aryl, heteroaryl, bicyclic-heteroaryl

As shown in Scheme XI, compounds of formula I can also be prepared from 15 by treatment with the defined amine in the presence of an acid catalyst (for example, see: Gunzenhauser et al., *Helv. Chim. Acta,* 71, 33 (1988)).

10 Utility

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The compounds of the present invention inhibit protein tyrosine kinases, especially Src-family kinases such as Lck, Fyn, Lyn, Src, Yes, Hck, Fgr and Blk, and are thus useful in the treatment, including prevention and therapy, of protein tyrosine kinase-associated disorders such as immunologic and oncologic disorders. The compounds inhibit also receptor tyrosine kinases including HER1 and HER2 and are therefore useful in the treatment of proliferative disorders such as psoriasis and cancer. The ability of these compounds to inhibit HER1 and other receptor kinases will also permit their use as anti-angiogenic agents to treat disorders such as cancer and diabetic retinopathy. "Protein tyrosine kinase-associated disorders" are those disorders which result from aberrant tyrosine kinase activity, and/or which are alleviated by the inhibition of one or more of these enzymes. For example, Lck inhibitors are of value in the treatment of a number of such disorders (for example, the treatment of autoimmune diseases), as Lck inhibition blocks T cell

activation. The treatment of T cell mediated diseases, including inhibition of T cell activation and proliferation, is a particularly preferred embodiment of the present invention. Compounds which selectively block T cell activation and proliferation are preferred. Compounds of the present invention which block the activation of endothelial cell PTK by oxidative stress, thereby limiting surface expression of adhesion molecules that induce neutrophil binding, and which inhibit PTK necessary for neutrophil activation are useful, for example, in the treatment of ischemia and reperfusion injury.

The present invention thus provides methods for the treatment of protein tyrosine kinase-associated disorders, comprising the step of administering to a subject in need thereof at least one compound of the formula I in an amount effective therefor. Other therapeutic agents such as those described below may be employed with the inventive compounds in the present methods. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

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Use of the compounds of the present invention in treating protein tyrosine kinase-associated disorders is exemplified by, but is not limited to, treating a range of disorders such as: transplant (such as organ transplant, acute transplant or heterograft or homograft (such as is employed in burn treatment)) rejection; protection from ischemic or reperfusion injury such as ischemic or reperfusion injury incurred during organ transplantation, myocardial infarction, stroke or other causes; transplantation tolerance induction; arthritis (such as rheumatoid arthritis, psoriatic arthritis or osteoarthritis); multiple sclerosis; chronic obstructive pulmonary disease (COPD), such as emphysema; inflammatory bowel disease, including ulcerative colitis and Crohn's disease; lupus (systemic lupus erythematosis); graft vs. host disease; T-cell mediated hypersensitivity diseases, including contact hypersensitivity,

delayed-type hypersensitivity, and gluten-sensitive enteropathy (Celiac disease); psoriasis; contact dermatitis (including that due to poison ivy); Hashimoto's thyroiditis; Sjogren's syndrome; Autoimmune Hyperthyroidism, such as Graves' Disease; Addison's disease (autoimmune disease of the adrenal glands); Autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome); autoimmune alopecia; pernicious anemia; vitiligo; autoimmune hypopituatarism; Guillain-Barre syndrome; other autoimmune diseases; cancers, including cancers where Lck or other Src-family kinases such as 10 Src are activated or overexpressed, such as colon carcinoma and thymoma, and cancers where Src-family kinase activity facilitates tumor growth or survival; glomerulonephritis; serum sickness; uticaria; allergic diseases such as respiratory allergies (asthma, hayfever, allergic rhinitis) or skin allergies; scleracierma; mycosis fungoides; acute inflammatory responses (such as acute respiratory distress syndrome and ishchemia/reperfusion 15 injury); dermatomyositis; alopecia areata; chronic actinic dermatitis; eczema; Behcet's disease; Pustulosis palmoplanteris; Pyoderma gangrenum; Sezary's syndrome; atopic dermatitis; systemic schlerosis; and morphea. The present invention also provides a method for treating 20 the aforementioned disorders such as atopic dermatitis by administration of any compound capable of inhibiting protein tyrosine kinase.

Src-family kinases other than Lck, such as Hck and Fgr, are important in the Fc gamma receptor responses of monocytes and macrophages. Compounds of the present invention inhibit the Fc gamma dependent production of TNF alpha in the monocyte cell line THP-1 that does not express Lck. The ability to inhibit Fc gamma receptor dependent monocyte and macrophage responses results in additional anti-inflammatory activity for the present compounds beyond their effects on T cells. This activity is especially of value, for example, in the treatment of inflammatory diseases such as arthritis or inflammatory bowel disease. In particular, the present compounds are of value for the treatment of

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autoimmune glomerulonephritis and other instances of glomerulonephritis induced by deposition of immune complexes in the kidney that trigger Fc gamma receptor responses leading to kidney damage.

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In addition, Src family kinases other than Lck, such as Lyn and Src, are important in the Fc epsilon receptor induced degranulation of mast cells and basophils that plays an important role in asthma, allergic rhinitis, and other allergic disease. Fc epsilon receptors are stimulated by IgE-antigen complexes. Compounds of the present invention inhibit the Fc epsilon induced degranulation responses, including in the basophil cell line RBL that does not express Lck. The ability to inhibit Fc epsilon receptor dependent mast cell and basophil responses results in additional anti-inflammatory activity for the present compounds beyond their effect on T cells. In particular, the present compounds are of value for the treatment of asthma, allergic rhinitis, and other instances of allergic disease.

The combined activity of the present compounds towards monocytes, macrophages, T cells, etc. may be of value in the treatment of any of the aforementioned disorders.

In a particular embodiment, the compounds of the present invention are useful for the treatment of the aforementioned exemplary disorders irrespective of their etiology, for example, for the treatment of transplant rejection, rheumatoid arthritis, multiple sclerosis, chronic obstructive pulmonary disease, inflammatory bowel disease, lupus, graft v. host disease, T-cell mediated hypersensitivity disease, psoriasis, Hashimoto's thyroiditis, Guillain-Barre syndrome, cancer, contact dermatitis, allergic disease such as allergic rhinitis, asthma, ischemic or reperfusion injury, or atopic dermatitis whether or not associated with PTK.

By virtue of their ability to inhibit HER1 and HER2 kinases, compounds of the present invention can also be used for the treatment of

proliferative diseases, including psoriasis and cancer. The HER1 receptor kinase has been shown to be expressed and activated in many solid tumors including non-small cell lung, colorectal, and breast cancer. Similarly, the HER2 receptor kinase has been shown to be overexpressed in breast, ovarian, lung and gastric cancer. Monoclonal antibodies that downregulate the abundance of the HER2 receptor or inhibit signaling by the HER1 receptor have shown anti-tumor effficacy in preclincal and clinical studies. It is therefore expected that inhibitors of the HER1 and HER2 kinases will have efficacy in the treatment of tumors that depend on signaling from either of the two receptors. These compounds are expected to have efficacy either as single agent or in combination with other chemotherapeutic agents such as placlitaxel (Taxol), doxorubicin hydrochloride (adriamycin), and cisplatin (Platinol). See the following documents and references cited therein: Cobleigh, M. A., Vogel, C. L., Tripathy, D., Robert, N. J., Scholl, S., Fehrenbacher, L., Wolter, J. M., Paton, V., Shak, S., Lieberman, G., and Slamon, D. J., "Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease", J. of Clin. Oncol. 17(9), p. 2639-2648 (1999); Baselga, J., Pfister, D., Cooper, M. R., Cohen, R., Burtness, B., Bos, M., D'Andrea, G., Seidman, A., Norton, L., Gunnett, K., Falcey, J., Anderson, V., Waksal, H., and Mendelsohn, J., "Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin", J. Clin. Oncol. 18(4), p. 904-914 (2000).

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The present invention also provides pharmaceutical compositions comprising at least one of the compounds of the formula I capable of treating a protein tyrosine kinase-associated disorder in an amount effective therefor, and a pharmaceutically acceptable vehicle or diluent. The compositions of the present invention may contain other therapeutic agents as described below, and may be formulated, for example, by

employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

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The compounds of the formula I may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds may also be administered liposomally.

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The present compounds may also be delivered through the oral cavity by sublingual and/or buccal administration.

Molded tablets, compressed tablets or freeze-dried tablets are exemplary

forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations may also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g., Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

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Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human of from about 0.1 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like, subject to protein tyrosine kinase-associated disorders.

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The compounds of the present invention may be employed alone or in combination with each other and/or other suitable therapeutic agents useful in the treatment of protein tyrosine kinase-associated disorders such as PTK inhibitors other than those of the present invention, antiinflammatories, antiproliferatives, chemotherapeutic agents, immunosuppressants, anticancer agents and cytotoxic agents.

Exemplary such other therapeutic agents include the following: cyclosporins (e.g., cyclosporin A), CTLA4-Ig, antibodies such as anti-ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, monoclonal antibody OKT3, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CD154), fusion proteins constructed from CD40 and gp39 (CD40Ig and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, steroids such as prednisone or dexamethasone, gold

compounds, antiproliferative agents such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil, cytotoxic drugs such as azathiprine and cyclophosphamide, TNF-α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor such as etanercept (Enbrel), 5 rapamycin (sirolimus or Rapamune), leflunimide (Arava), and cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx), or derivatives thereof, and the PTK inhibitors disclosed in the following U.S. Patent Applications, incorporated herein by reference in their entirety: Serial No. 60/056,770, filed 8/25/97 (Attorney Docket No. QA202\*), Serial No. 60/069,159, filed 12/9/97 (Attorney Docket No. 10 QA202a\*), Serial No. 09/097,338, filed 6/15/98 (Attorney Docket No. QA202b), Serial No. 60/056,797, filed 8/25/97 (Attorney Docket No. QA205\*), Serial No. 09/094,797, filed 6/15/98 (Attorney Docket No. QA205a), Serial No. 60/065,042, filed 11/10/97 (Attorney Docket No. 15 QA207\*), Serial No. 09/173,413, filed 10/15/98, (Attorney Docket No. QA207a), Serial No. 60,076,789, filed 3/4/98 (Attorney Docket No. QA208\*), and Serial No. 09,262,525, filed 3/4/99 (Attorney Docket No. QA208a). See the following documents and references cited therein: Hollenbaugh, D., Douthwright, J., McDonald, V., and Aruffo, A., **20** "Cleavable CD40Ig fusion proteins and the binding to sgp39", J. Immunol. Methods (Netherlands), 188(1), p. 1-7 (Dec 15 1995); Hollenbaugh, D., Grosmaire, L.S., Kullas, C.D., Chalupny, N.J., Braesch-Andersen, S., Noelle, R.J., Stamenkovic, I., Ledbetter, J.A., and Aruffo, A., "The human T cell antigen gp39, a member of the TNF gene family, is a ligand for the 25 CD40 receptor: expression of a soluble form of gp39 with B cell costimulatory activity", *EMBO J* (England), 11(12), p 4313-4321 (Dec 1992); and Moreland, L.W. et al., "Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion

Exemplary classes of anti-cancer agents and cytotoxic agents include, but are not limited to: alkylating agents, such as nitrogen

protein, New England J. of Medicine, 337(3), p. 141-147 (1997).

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mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes; antimetabolites, such as folate antagonists, purine analogues, and pyrimidine analogues; antibiotics, such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes, such as L-asparaginase; farnesyl-protein transferase inhibitors; hormonal agents, such as glucocorticoids, estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone anatagonists, octreotide acetate; microtubule-disruptor agents, such as ecteinascidins or their analogs and derivatives; microtubule-stabilizing agents such as paclitaxel (Taxol®), docetaxel (Taxotere®), and epothilones A-F or their analogs or derivatives; plant-derived products, such as vinca alkaloids, epipodophyllotoxins, taxanes; and topoisomerase inhibitors; prenyl-protein transferase inhibitors; and miscellaneous agents such as, hydroxyurea, procarbazine, mitotane, hexamethylmelamine, platinum coordination complexes such as cisplatin and carboplatin; and other agents used as anti-cancer and cytotoxic agents such as biological response modifiers, growth factors; immune modulators, and monoclonal antibodies. The compounds of the invention may also be used in conjunction with radiation therapy.

Representative examples of these classes of anti-cancer and cytotoxic agents include, but are not limited to, mechlorethamine hydrochlordie, cyclophosphamide, chlorambucil, melphalan, ifosfamide, busulfan, carmustin, lomustine, semustine, streptozocin, thiotepa, dacarbazine, methotrexate, thioguanine, mercaptopurine, fludarabine, pentastatin, cladribin, cytarabine, fluorouracil, doxorubicin hydrochloride, daunorubicin, idarubicin, bleomycin sulfate, mitomycin C, actinomycin D, safracins, saframycins, quinocarcins, discodermolides, vincristine, vinblastine, vinorelbine tartrate, etoposide, teniposide, paclitaxel, tamoxifen, estramustine,

estramustine phosphate sodium, flutamide, buserelin, leuprolide, pteridines, diyneses, levamisole, aflacon, interferon, interleukins, aldesleukin, filgrastim, sargramostim, rituximab, BCG, tretinoin, irinotecan hydrochloride, betamethosone, gemcitabine hydrochloride, altretamine, and topoteca and any analogs or derivatives thereof.

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Preferred members of these classes include, but are not limited to paclitaxel, cisplatin, carboplatin, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, mitomycin C, ecteinascidin 743, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, and leurosine.

Examples of anti-cancer and other cytotoxic agents include the following: epothilone derivatives as found in U.S. Serial No. 09/506,481 filed February 17, 2000 (Attorney Docket No. LD186); German Patent No. 4138042.8; WO 97/19086, WO 98/22461, WO 98/25929, WO 98/38192, WO 99/01124, WO 99/02224, WO 99/02514, WO 99/03848, WO 99/07692, WO 99/27890, WO 99/28324, WO 99/43653, WO 99/54330, WO 99/54318, WO 99/54319, WO 99/65913, WO 99/67252, WO 99/67253, and WO 00/00485; cyclin dependent kinase inhibitors as found in WO 99/24416; and prenyl-protein transferase inhibitors as found in WO 97/30992 and WO 98/54966.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

The following assays can be employed in ascertaining the degree of activity of a compound ("test compound") as a PTK inhibitor.

Compounds described in the following Examples have been tested in one or more of these assays, and have shown activity.

Enzyme Assay Using Lck, Fyn, Lyn, Hck, Fgr, Src, Blk or Yes

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The following assay has been carried out using the protein tyrosine kinases *Lck*, *Fyn*, *Lyn*, *Hck*, *Fgr*, *Src*, *Blk* and *Yes*.

The protein tyrosine kinase of interest is incubated in kinase buffer (20 mM MOPS, pH7, 10 mM MgCl<sub>2</sub>) in the presence of the test compound. The reaction is initiated by the addition of substrates to the final concentration of 1 µM ATP, 3.3 µCi/ml [33P] gamma-ATP, and 0.1 mg/ml acid denatured enolase (prepared as described in Cooper, J.A., Esch, F.S., Taylor, S.S., and Hunter, T., "Phosphorylation sites in enclase and lactate dehydrogenase utilized by tyrosine protein kinases in vivo and in vitro", J. Biol. Chem., 259, 7835-7841 (1984)). The reaction is stopped after 10 minutes by the addition of 10% trichloroacetic acid, 100 mM sodium pyrophosphate followed by 2 mg/ml bovine serum albumin. The labeled enolase protein substrate is precipitated at 4 degrees, harvested onto Packard Unifilter plates and counted in a Topcount scintillation counter to ascertain the protein tyrosine kinase inhibitory activity of the test compound (activity inversely proportional to the amount of labeled enolase protein obtained). The exact concentration of reagents and the amount of label can be varied as needed.

This assay is advantageous as it employs an exogenous substrate (enolase) for more accurate enzyme kinetics, and can be conducted in a 96-well format that is readily automated. In addition, His-tagged protein tyrosine kinases (described below) offer much higher production yields and purity relative to GST-protein tyrosine kinase fusion protein.

The protein tyrosine kinase may be obtained from commercial sources or by recombinant methods described herewith. For the preparation of recombinant Lck, human Lck was prepared as a His-tagged fusion protein using the Life Technologies (Gibco) baculovirus vector

pFastBac Hta (commercially available) in insect cells. A cDNA encoding human Lck isolated by PCR (polymerase chain reaction) was inserted into the vector and the protein was expressed using the methods described by the manufacturer. The Lck was purified by affinity chromatography. For the production of Lck in insect cells using baculovirus, see Spana, C., O'Rourke, E.C., Bolen, J.B., and Fargnoli, J., "Analysis of the tyrosine kinase p56lck expressed as a glutathione S-transferase protein in Spodoptera frugiperda cells," Protein expression and purification, Vol. 4, p. 390-397 (1993). Similar methods may be used for the recombinant production of other Src-family kinases.

Enzyme Assay Using HER1 or HER2

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Compounds of interest were assayed in a kinase buffer that contained 20 mM Tris.HCl, pH 7.5, 10 mM MnCl<sub>2</sub>, 0.5 mM dithiothreitol, bovine serum albumin at 0.1 mg/ml, poly(glu/tyr, 4:1) at 0.1 mg/ml, 1µM ATP, and 4 µCi/ml [gamma-<sup>33</sup>P]ATP. Poly(glu/tyr, 4:1) is a synthetic polymer that serves as a phosphoryl acceptor and is purchased from Sigma Chemicals. The kinase reaction is initiated by the addition of enzyme and the reaction mixtures were incubated at 26°C for 1 h. The reaction is terminated by the addition of EDTA to 50 mM and proteins are precipitated by the addition of trichloroacetic acid to 5%. The precipitated proteins are recovered by filtration onto Packard Unifilter plates and the amount of radioactivity incorporated is measured in a Topcount scintillation counter.

For the preparation of recombinant HER1, the cytoplasmic sequence of the receptor were expressed in insect cells as a GST fusion protein, which was purified by affinity chromatography as described above for Lck. The cytoplasmic sequence of HER2 was subcloned into the baculovirus expression vector pBlueBac4 (Invitrogen) and was expressed as an untagged protein in insect cells. The recombinant protein was partially purified by ion-exchange chromatography.

Cell assays

### (1) Cellular tyrosine phosphorylation

Jurkat T cells are incubated with the test compound and then stimulated by the addition of antibody to CD3 (monoclonal antibody G19-

4). Cells are lysed after 4 minutes or at another desired time by the addition of a lysis buffer containing NP-40 detergent. Phosphorylation of proteins is detected by anti-phosphotyrosine immunoblotting. Detection of phosphorylation of specific proteins of interest such as ZAP-70 is detected by immunoprecipitation with anti-ZAP-70 antibody followed by anti-phosphotyrosine immunoblotting. Such procedures are described in Schieven, G.L., Mittler, R.S., Nadler, S.G., Kirihara, J.M., Bolen, J.B., Kanner, S.B., and Ledbetter, J.A., "ZAP-70 tyrosine kinase, CD45 and T cell receptor involvement in UV and H<sub>2</sub>O<sub>2</sub> induced T cell signal transduction", J. Biol. Chem., 269, 20718-20726 (1994), and the references incorporated therein. The Lck inhibitors inhibit the tyrosine

For the preparation of G19-4, see Hansen, J.A., Martin, P.J., Beatty, P.G., Clark, E.A., and Ledbetter, J.A., "Human T lymphocyte cell surface molecules defined by the workshop monoclonal antibodies," in *Leukocyte Typing I*, A. Bernard, J. Boumsell, J. Dausett, C. Milstein, and S. Schlossman, eds. (New York: Springer Verlag), p. 195-212 (1984); and Ledbetter, J.A., June, C.H., Rabinovitch, P.S., Grossman, A., Tsu, T.T., and Imboden, J.B., "Signal transduction through CD4 receptors: stimulatory vs. inhibitory activity is regulated by CD4 proximity to the

phosphorylation of cellular proteins induced by anti-CD3 antibodies.

25 CD3/T cell receptor", Eur. J. Immunol., 18, 525 (1988).

#### (2) Calcium assay

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Lck inhibitors block calcium mobilization in T cells stimulated with anti-CD3 antibodies. Cells are loaded with the calcium indicator dye indo1, treated with anti-CD3 antibody such as the monoclonal antibody G19-4, and calcium mobilization is measured using flow cytometry by recording

changes in the blue/violet indo-1 ratio as described in Schieven, G.L., Mittler, R.S., Nadler, S.G., Kirihara, J.M., Bolen, J.B., Kanner, S.B., and Ledbetter, J.A., "ZAP-70 tyrosine kinase, CD45 and T cell receptor involvement in UV and H<sub>2</sub>O<sub>2</sub> induced T cell signal transduction", J. Biol. Chem., 269, 20718-20726 (1994), and the references incorporated therein.

#### (3) Proliferation assays

Lck inhibitors inhibit the proliferation of normal human peripheral blood T cells stimulated to grow with anti-CD3 plus anti-CD28 antibodies.

A 96 well plate is coated with a monoclonal antibody to CD3 (such as G19-4), the antibody is allowed to bind, and then the plate is washed. The antibody bound to the plate serves to stimulate the cells. Normal human peripheral blood T cells are added to the wells along with test compound plus anti-CD28 antibody to provide co-stimulation. After a desired period of time (e.g., 3 days), the [3H]-thymidine is added to the cells, and after further incubation to allow incorporation of the label into newly synthesized DNA, the cells are harvested and counted in a scintillation counter to measure cell proliferation.

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The following Examples illustrate embodiments of the present invention, and are not intended to limit the scope of the claims.

Abbreviations employed in the Examples are defined below. Compounds of the Examples are identified by the example and step in which they are prepared (for example, "1A" denotes the title compound of step A of Example 1), or by the example only where the compound is the title compound of the example (for example, "2" denotes the title compound of Example 2).

#### **Abbreviations**

aq. = aqueous

5 conc. = concentrated

DMSO = dimethylsulfoxide

EtOAc = ethyl acetate

 $Et_2O = diethyl ether$ 

h = hours

10 HATU = N-[dimethylamino-1H-1,2,3-triazolo-[4,5-b]pyridin-1-yl methylene]-N-methyl methanaminium hexafluorophosphate N-oxide

MeOH = methanol

MOPS = 4-morpholine-propanesulfonic acid

15 MS = mass spectrometry

Ret Time = retention time

RT = room temperature

satd. = saturated

TFA = trifluoroacetic acid

20 THF = tetrahydrofuran

DMF= N,N-dimethylformamide

#### Example 1

<u>Preparation of [5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester</u>

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A. Ethyl-2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate
A suspension of ethyl-2-amino-4-methyl-thiazole-5-carboxylate (18.6 g, 100 mmol), di-t-butyldicarbonate (26.2 g, 120 mmol) and 4-dimethylaminopyridine (800 mg, 6.55 mmol) in dry tetrahydrofuran (300 mL) was stirred under nitrogen for 18 h. The solvent was evaporated in vacuo. The residue was suspended in dichloromethane (1 L) and filtered through a pad of celite. The filtrate was washed with 1 N aqueous HCl solution (300 mL, 2x), water and brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo. The residue was triturated with hexanes. The solid was filtered and dried in vacuo to obtain the title compound (20 g, 72%) as a tan solid.

B. 2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid A stirred solution of ethyl-2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate (10 g, 34.95 mmol) in tetrahydrofuran-ethanol (250 mL, 2:3) was treated with a 6N KOH solution (250 mL). The mixture was heated to 55°C overnight. The solution was cooled to 0°C and acidified with concd. HCl to pH 1. The solvent was evaporated in vacuo. The residue was washed with water, diethyl ether, dried in vacuo over anhydrous phosphorous pentoxide to obtain the title acid (6 g, 89%) as a white solid.

# C. 2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid chloride

A 2 M solution of oxalyl chloride in dichloromethane (22.5 mL, 45 mmol) was added dropwise to a stirred suspension of 2-tert-

butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid (10 g, 38.72 mmol) in dichloromethane (150 mL) and N,N-dimethyl formamide (150 μL) at 0°C. The suspension gradually became homogenous after addition was complete. The solution was allowed to warm to room temperature and stirred at rt for 1.5 h. The solvent was evaporated in vacuo and the
 residue was coevaporated with toluene (300 mL, 2x) and then dried in vacuo to obtain the title acid chloride (10.7 g, 99%) as a tan solid.

# D. [5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

2,4,6-Trimethyl aniline (6.3 mL, 38.66 mmol) was added dropwise to a stirred solution of 2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid chloride (10.7 g, 38.66 mmol) in dichloromethane (150 mL) at 0°C. After 20 min, diisopropylethylamine (8.8 mL, 44.88 mmol) was added dropwise. The solution was allowed to warm to rt and stirred for an additional 2 h. The solvent was evaporated in vacuo. The residue was suspended in EtOAc (700 mL), washed with 1 N aq. HCl solution (300 mL, 2x), water, and brine; dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was triturated with ether to obtain the title compound (12.5 g, 86%) as a tan solid.

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#### Example 2

## Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-methyl-5thiazolecarboxamide

A solution of [5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester (10 g, 26.63 mmol) in trifluoroacetic acid (100 mL) was stirred at rt for 3 h. The solution was concentrated under reduced pressure and the residue was diluted with EtOAc (700 mL), washed with 5% aq. KHCO<sub>3</sub> solution (400 mL, 2x), water, and brine; dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was washed with ether (200 mL) and acetonitrile (100 mL) to obtain the title compound (6.7 g, 91%) as a white solid.

#### Example 3

<u>Preparation of [5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-trifluoromethyl-2-thiazolyllcarbamic acid, 1,1-dimethylethyl ester</u>

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A. Ethyl-2-tert-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylate

A suspension of ethyl-2-amino-4-trifluoromethyl-thiazole-5-carboxylate (5.05 g, 21.02 mmol), di-t-butyldicarbonate (4.82 g, 22.07 mmol) and 4-dimethylaminopyridine (260 mg, 2.1 mmol) in dichloromethane (209 mL) was stirred under nitrogen for 1.5 h. The solvent was evaporated *in vacuo*. The residue was chromatographed on a silica gel column. Elution with 5% EtOAc in hexanes, followed by 15% EtOAc in hexanes afforded the title compound (6.57 g, 92%) as a white solid.

B. 2-Tert-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylic acid

A stirred solution of ethyl-2-tert-butoxycarbonyloxyamino-4-

trifluoromethyl-thiazole-5-carboxylate (6.5 g, 19.1 mmol) in methanol (100 mL) was treated with a 1N aq. NaOH solution (573 mL). The mixture was stirred at rt overnight. The solution was cooled to 0°C and acidified with a 6 M aq. HCl solution to pH 1 and extracted with chloroform (150 mL, 6x). The chloroform extracts were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure and in vacuo to obtain the title acid (5.75 g, 96%) as a white solid.

# C. [5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-trifluoromethyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

- 4-Methylmorpholine (40 μL, 0.39 mmol) was added to a mixture of 2-tert-butoxycarbonyloxyamino-4-trifluoromethyl-thiazole-5-carboxylic acid (100 mg, 0.32 mmol), 2,4,6-trimethylaniline (45 μL, 0.32 mmol), and benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP reagent, 380 mg, 0.4 mmol) in DMF (2 mL).
- The solution was stirred at rt for 72 h, diluted with dichloromethane and washed with 0.25 M aq. KHSO<sub>4</sub> solution followed by satd. aq. KHCO<sub>3</sub> solution. The dichloromethane extract was separated, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 5% EtOAc in hexanes followed by 10% EtOAc in hexanes to obtain the title compound (00 mg. 65%) as a white solid.

## in hexanes to obtain the title compound (90 mg, 65%) as a white solid.

#### Example 4

Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-trifluoromethyl-5thiazolecarboxamide, trifluoroacetate (1:1)

A solution of [5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-trifluoromethyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester (120 mg, 0.28 mmol) in trifluoroacetic acid (5 mL) was stirred at 0°C for 1 h. The solution was concentrated under reduced pressure and the residue was coevaporated with ether to obtain a yellow solid which was triturated with hexanes to obtain the title compound (96 mg, 76%) as a light yellow solid.

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#### Example 5

Preparation of [5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-phenyl-2thiazolyl]carbamic acid, 1,1-dimethylethyl ester

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A. Ethyl-2-tert-butoxycarbonyloxyamino-4-phenyl-thiazole-5-carboxylate Compound 5A was prepared by an analogous method as that of 3A, except using ethyl-2-amino-4-phenyl-thiazole-5-carboxylate to give the title compound 5A as a white solid (90.5%).

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B. 2-Tert-butoxycarbonyloxyamino-4-phenyl-thiazole-5-carboxylic acid Compound **5B** was prepared by an analogous method as that of **3B**, except using **5A** to give the title compound **5B** as a white solid (99%).

C. 2-Tert-butoxycarbonyloxyamino-4-phenyl-thiazole-5-carboxylic acid chloride

Compound 5C was prepared by an analogous method as that of 1C, except using 5B to give the title compound 5C as a white solid (90%).

D. [5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-phenyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

Compound **5D** was prepared by an analogous method as that of **1D**, except using **5C** to give the title compound **5D** as a light yellow solid (93%).

# Example 6 Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-phenyl-5thiazolecarboxamide, trifluoroacetate (1:1)

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Compound 6 was prepared by an analogous method as that of 4, except using 5D to give the title compound 6 as a white solid (68%).

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#### Example 7

<u>Preparation of [5-[[Phenylamino]carbonyl]-4-methyl-2-thiazolyl]carbamic</u>

<u>acid, 1,1-dimethylethyl ester</u>

Compound was prepared by an analogous method as that of 1D, except using aniline in place of 2,4,6-trimethylaniline and triethylamine in place of disopropylethylamine to give the title compound 7 as an off-white solid (76%).

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#### Example 8

## Preparation of 2-Amino-N-(phenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1)

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Compound 8 was prepared by an analogous method as that of 4, except using 7 to give the title compound 8 as a white solid (68%).

#### Example 9

# Preparation of [5-[[(2,4-Dichlorophenyl)amino]carbonyl]-4-methyl-2thiazolyl]carbamic acid, 1,1-dimethylethyl ester

Compound **9** was prepared by an analogous method as that of **1D**, except using 2,4-dichloroaniline to give the title compound **9** as a white solid (28%).

#### Example 10

Preparation of 2-Amino-N-(2,4-dichlorophenyl)-4-methyl-5thiazolecarboxamide, trifluoroacetate (1:1)

Compound 10 was prepared by an analogous method as that of 4, except using 9 to give the title compound 8 as a white solid (100%).

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#### Example 11

# <u>Preparation of 5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-2-</u> <u>thiazolyl]carbamic acid, 1,1-dimethylethyl ester</u>

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A. Ethyl-2-tert-butoxycarbonyloxyamino-thiazole-5-carboxylate Compound 11A was prepared by an analogous method as that of 3A, except using ethyl-2-amino-thiazole-5-carboxylate to give the title compound 11A as a white solid (79.5%).

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- B. 2-Tert-butoxycarbonyloxyamino -thiazole-5-carboxylic acid
  Compound 11B was prepared by an analogous method as that of 3B,
  except using 11A to give the title compound 11B as a white solid (95.5%).
- 20 <u>C. 2-Tert-butoxycarbonyloxyamino-thiazole-5-carboxylic acid chloride</u> Compound 11C was prepared by an analogous method as that of 1C, except using 11B to give the title compound 11C.
- D. [5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid,
  25 1,1-dimethylethyl ester

Compound 11D was prepared by an analogous method as that of 1D, except using 11C to give the title compound 11D as an off-white solid (70%).

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#### Example 12

# Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-phenyl-5thiazolecarboxamide, trifluoroacetate (1:1)

Compound 12 was prepared by an analogous method as that of 4, except using 11D to give the title compound 12 as a light yellow solid (88%).

#### Examples 13 to 53

General Procedure

15 Compounds 13 to 53 were prepared following the procedure described below. Appropriate amines (0.40 mmol) and diisopropylethylamine (70 µL, 0.40 mmol) were added to a suspension of 1C (100 mg, 0.36 mmol) in dichloromethane (3 mL). The solution was stirred mechanically in a sealed tube at rt for 16 h. The reaction mixtures were diluted with methanol (200 μL) and loaded in Varian SCX ion exchange columns (2 g/6 cc) pretreated 20 with methanol-dichloromethane (8 mL, 1:1) followed by dichloromethane (8 mL). SCX Column filtration were performed using a Gilson robot unit. The column was washed sequentially with dichloromethane (9 mL), dichloromethane-methanol (9 mL, 4:1), dichloromethane-methanol (9 mL, 25 1:1), methanol (9 mL), 0.01 M ammonium hydroxide in methanol (9 mL) and 0.05 M ammonium hydroxide in methanol (9 mL). The elutes were collected separetely by the robot and then concentrated using a speed vac. Fractions containing the products were combined.

"HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90%  $H_2O$ , 0.2%  $H_3PO_4$ ) to 100% solvent B (90% MeOH, 10%  $H_2O$ , 0.2%  $H_3PO_4$ ), flow rate 4 mL/min,  $\lambda$  = 220 nM.

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EX.	Compound Structure	Compound No	lupi o
i	Compound Structure	Compound Name	HPLC
NO.			Ret Time
· .			(min)
13	H <sub>3</sub> C, O CH <sub>3</sub> N O CH <sub>3</sub> CH <sub>3</sub>	[5-[[(2-Methoxy-6-methylphenyl)amino]-carbonyl]-4-methyl-2-thiazolyl]carbamicacid 1,1-dimethylethylester	3.79
14	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	[4-Methyl-5-[[[3-methyl-4-(1-methyl-ethyl)phenyl] amino]-carbonyl]-2-thiazolyl]-carbamic acid 1,1-dimethylethylester	4.51
15	H <sub>3</sub> C CH <sub>3</sub> Br  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	[5-[[(4-Bromo-2,6-di-methylphenyl)amino]-carbonyl]-4-methyl-2-thiazolyl]carbamicacid 1,1-dimethyl-ethyl ester	4.24
16	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	[4-Methyl-5-[[[2-methyl-6-(1-methylethyl)phenyl]-amino]carbonyl]-2-thiazolyl]carbamicacid 1,1-dimethylethylester	4.17

17	ш.с	IE   I   12   A	4.05
17	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> S N	[5-[[(2,4-Dimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamicacid 1,1-dimethylethyl	4.05
	H <sub>3</sub> C CH <sub>3</sub>	ester	
18	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	[4-Methyl-5-[[(2-methylphenyl)amino]carbonyl]-2-thiazolyl]carbamicacid 1,1-dimethylethylester	3.87
19	CH <sub>3</sub> C N O CH <sub>3</sub> N S N O CH <sub>3</sub> CH <sub>3</sub>	[5-[[(2-Chloro-6-methylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamicacid 1,1-dimethylethylester	3.86
20	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	[5-[[2-(1,1-Dimethylethyl)-4-methylphenyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamicacid 1,1-dimethylethylester	4.30
21	H <sub>3</sub> C	[5-[[(2-Furanylmethyl)amino]ca rbonyl]-4-methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.54
22	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C N F F H <sub>3</sub> C N F F	[5-[[[3-Methoxy-5- (trifluoromethyl)pheny l]amino]carbonyl]-4- methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.43
لـــــــــــــــــــــــــــــــــــــ	130		

24  24  CH3  CH3  CH3  CH3  CH3  CH3  CH3  CH				
methyl)amino]carbonyl] -4-methyl-2-thiazolyl] carbamic acid 1,1- dimethylethyl ester  25  H <sub>3</sub> C, N, O, CH <sub>3</sub> H <sub>3</sub> C, CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> [5-[(2,3-Dihydro-1H- indenyl)amino]carbonyl] -4-methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl ester  26  [5-[(2,5-Dihydro-1H- pyrrol-1-yl)carbonyl]- 4-methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl ester  27  H <sub>3</sub> C, CH <sub>3</sub> [5-[(2,5-Dihydro-2,5- dimethyl-1H-pyrrol-1- yl)carbonyl]-4-methyl- 2-thiazolyl]carbamic acid 1,1-dimethylethyl ester  28  Abs  Abs  Abs  Abs  Abs  Abs  Acc  CH <sub>3</sub> Acc  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> Abs  Acc  CH <sub>3</sub> Acc  CH <sub>3</sub>	23	H <sub>2</sub> C Q X X Y	Cyclohexylphenyl)amino carbonyl]-4-methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl	
indenyl) amino] carbonyl  -4-methyl-2- thiazolyl] carbamic acid 1,1-dimethylethyl ester  [5-[(2,5-Dihydro-1H- pyrrol-1-yl) carbonyl]- 4-methyl-2- thiazolyl] carbamic acid 1,1-dimethylethyl ester  [5-[(2,5-Dihydro-2,5- dimethyl-1H-pyrrol-1- yl) carbonyl]-4-methyl- 2-thiazolyl] carbamic acid 1,1-dimethylethyl ester  [5-[(2,5-Dihydro-2,5- dimethyl-1H-pyrrol-1- yl) carbonyl]-4-methyl- 2-thiazolyl] carbamic acid 1,1-dimethylethyl ester  [5-[(1,1- Dimethylethoxy) carbony 1] amino] -4-methyl-5- thiazolyl] carbonyl]-1- prolinamide  [5-[(4-Formyl-1- piperazinyl) carbonyl]-4- methyl-2- thiazolyl] carbamic acid 1,1-dimethylethyl	24	N S N CH <sub>3</sub> CH <sub>3</sub>	methyl)amino]carbonyl] -4-methyl-2-thiazolyl] carbamic acid 1,1-	4.21
pyrrol-1-yl)carbonyl]- 4-methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl ester  27  H <sub>3</sub> C H <sub></sub>	25	H <sub>3</sub> C , 9 × CH <sub>3</sub>	<pre>indenyl)amino]carbonyl ]-4-methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl</pre>	4.30
dimethyl-1H-pyrrol-1- yl) carbonyl] -4-methyl- 2-thiazolyl] carbamic acid 1,1-dimethylethyl ester  28  Abs  Abs  Abs  Abs  Abs  Abs  Abs  Ab	26	H <sub>3</sub> C N	<pre>pyrrol-1-yl)carbonyl]- 4-methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl</pre>	3.56
Dimethylethoxy) carbony 1] amino] -4-methyl-5-thiazolyl] carbonyl]-L-prolinamide  29  H <sub>3</sub> C H <sub>3</sub>	27	H <sub>3</sub> C O N S	<pre>dimethyl-1H-pyrrol-1- yl)carbonyl]-4-methyl- 2-thiazolyl]carbamic acid 1,1-dimethylethyl</pre>	3.86
piperazinyl)carbonyl]-  4-methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl	28	H <sub>3</sub> C O N S O O O O O O O O O O O O O O O O O	Dimethylethoxy)carbony l]amino]-4-methyl-5- thiazolyl]carbonyl]-L-	2.96
	29	H <sub>3</sub> C N S O CH <sub>3</sub> C	piperazinyl)carbonyl]- 4-methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl	2.90

30	ǰ	[5-(1,4-Dioxa-8- azaspiro[4.5]decan-8-	3.54
·	H <sub>3</sub> C N CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	ylcarbonyl)-4-methyl- 2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	
31	H <sub>3</sub> C N O S N O CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	[5-[[3-[(Diethylamino) carbonyl]-1-piperidinyl] carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethylester	3.66
32	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> N H <sub>3</sub> C CH <sub>3</sub>	[4-Methyl-5- [(octahydro-1- quinolinyl)carbonyl]- 2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.37
33	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[[(1,1- Dimethylethoxy) carbonyl]amino]-4- methyl-5- thiazolecarboxylic acid 2-[(1,1- dimethylethoxy) carbonyl]hydrazide	3.50
34	H <sub>3</sub> C CH <sub>3</sub> N N CH <sub>3</sub> CH <sub>3</sub>	[5-[[(4-Methoxyphenyl) amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.83
35	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> N N N N N N N N N N N N N N N N N N N	[4-Methyl-5-[[(4-methylphenyl)amino]carbonyl]-2-thiazolyl]carbamicacid 1,1-dimethylethylester	4.07

36	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	[5-[[(1,2-Dimethylpropyl) amino]carbonyl]-4- methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.87
37	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> O CH <sub>3</sub>	[5-[[(2,2-Dimethylpropyl) amino]carbonyl]-4- methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.97
38	H <sub>3</sub> C CH <sub>3</sub> CCH <sub></sub>	[4-Methyl-5-[(2-propynylamino)carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethylester	3.22
39	H <sub>2</sub> C H <sub>3</sub> C O N S O O O O O O O O O O O O O O O O O	[4-Methyl-5-[(2-propenylamino)carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethylester	3.41
40	H <sub>3</sub> C CH <sub>3</sub>	[4-Methyl-5- [(methylphenylamino) carbonyl]-2- thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.75
41	CH <sub>3</sub>	[4-Methyl-5-[[(3,4,5-trimethoxyphenyl)amino]carbonyl]-2-thiazolyl]carbamicacid 1,1-dimethylethylester	3.84

42	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	[5-[[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]-4-methyl-2-thiazolyl]carbamicacid 1,1-dimethylethylester	4.40
43	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> N N N N N N N N N N N N N N N N N N	[5-[[[3-(1H-Imidazol- 1- yl)propyl]amino]carbon yl]-4-methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl ester	2.45
44	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C O N F F	[5-[[(3,4-Difluorophenyl)methyl] amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid 1,1-dimethylethylester	3.97
45	CH <sub>3</sub>	N-[[2-[[(1,1- Dimethylethoxy)carbony 1]amino]-4-methyl-5- thiazolyl]carbonyl]-L- leucine methyl ester	3.99
46	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	5-[[[2-[[(1,1-Dimethylethoxy)carbony]]amino]-4-methyl-5-thiazolyl]carbonyl]amino]-4-oxopentanoicacid methyl ester	3.27

[4=	1		<del></del>
47	H <sub>3</sub> C N S N N S N N S N N S N N S N N S N N S N N S N N S N N S N N S N S N N S N	[5-[[[2-(Ethylthio) ethyl]amino]carbonyl]- 4-methyl-2-thiazolyl] carbamic acid 1,1- dimethylethyl ester	3.75
48	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	[5-[[Bis(3-	4.67
	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	methylbutyl)amino]carb onyl]-4-methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl ester	4.07
49	H <sub>3</sub> C N S N O CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub>	[5-[[Ethyl(1-methylethyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamicacid 1,1-dimethylethylester	3.84
50	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C O O O O O O O O O O O O O O O O O O O	2-[[(1,1- Dimethylethoxy)carbony l]amino]-4-methyl-5- thiazolecarboxylic acid 2-[[(3,5- dichlorophenyl)amino]t hioxomethyl]hydrazide	4.66
51	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	[5-[[Bis(2- ethoxyethyl)amino]carb onyl]-4-methyl-2- thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.83
52		[4-Methyl-5-[[3- [(trifluoroacetyl)amin o]-1- pyrrolidinyl]carbonyl] -2-thiazolyl]carbamic acid 1,1-dimethylethyl ester	3.47

#### Examples 54 to 129

#### General Procedure

Compounds 54 to 129 were prepared following the procedure described below. Diisopropylethyl amine (60 µL, 0.34 mmol) was added to a mixture of amine 2 (30 mg, 0.11 mmol), appropriate carboxylic acid (0.13 mmol), 1hydroxy-7-azabenzotriazole (19.5 mg, 0.14 mmol), and ethyl-3-(3dimethylamino)-propyl carbodiimide hydrochloride (26.8 mg, 0.14 mmol) in THF (0.4 mL). The mixture was heated in a sealed tube under argon at 45°C for 24 h. The reaction mixture was diluted with dichloromethane (4 10 mL) and washed with 2 N aq. HCl solution (2 mL, 3x). The dichloromethane solution was passed through a Varian SCX cation exchange column (2 g, 6 cc) on a Gilson robot. The column was eluted sequentially with acetonitrile-methanol (10 mL, 4:1), methanol-2M 15 methanolic ammonia (3 mL, 4:1), and 2 M methanolic ammonia solution (3 mL, 4x). The fractions were collected separately using the Gilson robot. Fraction containing the product was concentrated and dried in vacuo. "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H,O, 0.2% H,PO,) to 100% 20 solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 4 mL/min,  $\lambda = 220$ nM for compounds 54 - 127. For compounds 128 -129 HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short column, 8 min gradient starting from 100% solvent A (10% MeOH, 90% H,O, 0.2% H,PO, ) to 100% solvent B (90% MeOH, 10%  $H_2O$ , 0.2%  $H_3PO_4$ ), flow rate 2.5 mL/min,  $\lambda = 217$  nM. 25

EX.	Compound Structure	Compound Name	HPLC
NO.			Ret Time
54	H <sub>3</sub> C N S CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[[(2,2-Dichloro-1-methylcyclopropyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	(min) 4.22
55	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[(Cyclohexyl acetyl)amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.47
56	F O CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[(2,5-Difluoro- benzoyl)amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.15
57	Br CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[(5-Bromo-2- chlorobenzoyl)amino]- 4-methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.37
58	CH <sub>3</sub>	2-[(3-Cyano- benzoyl)amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.06
59	H <sub>3</sub> C CH <sub>3</sub>	2-[[4-(Acetylamino)- benzoyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.60

60	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	Chiazorecarboxamide	4.45
61	CH <sub>3</sub> CH <sub>3</sub> C N-S N-CH <sub>3</sub> CH <sub>3</sub>	4-Methyl-2-[[2-(2-phenylethyl)benzoyl]-amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.64
62	H <sub>3</sub> C OH <sub>3</sub> C CH <sub>3</sub>	2-[(3,5-Dimethyl-benzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.49
63	H <sub>2</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[(4-Ethenyl- benzoyl)amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	
64	H <sub>3</sub> CCCH <sub>3</sub> CH <sub>3</sub>		4.58
65	H <sub>3</sub> C (CH <sub>3</sub>	4-Methyl-2-[(4- pentylbenzoyl)amino]- N-(2,4,6-trimethyl- phenyl)-5-thiazole- carboxamide	4.76

	T 211		
66	H <sub>3</sub> C	4-Methyl-2-[(2-methyl- 1-oxohexyl)amino]-N- (2,4,6-trimethyl- phenyl)-5-thiazole- carboxamide	4.41
67	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	4-Methyl-2-[(1-oxo-3-phenoxypropyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.21
68	S CH <sub>3</sub>	4-Methyl-2-[(1-oxo-3-phenylpropyl)amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.26
69	CH <sub>3</sub>	2-[[3-(2-Methoxy- phenyl)-1-oxopropyl]- amino]-4-methyl-N- (2,4,6-trimethyl- phenyl)-5-thiazole- carboxamide	4.31
70	CH <sub>0</sub>	4-Methyl-2-[(2- naphthalenylacetyl)- amino]-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.43
71	CH <sub>3</sub> C <sub>N</sub> NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	2-[(Diphenyl- acetyl)amino]-4- methyl-N-(2,4,6- crimethylphenyl)-5- chiazolecarboxamide	4.13
72	F CH <sub>3</sub>	-[[(2-Chloro-6- luorophenyl)acetyl]- mino]-4-methyl-N- 2,4,6-trimethyl- henyl)-5-thiazole- arboxamide	4.17

73		4-Methyl-2-[[(2-	3.95
1.3	CH₃	methylphenyl) -	5.55
		acetyl]amino]-N-	
	N CH <sub>3</sub>	(2,4,6-trimethyl-	
	N NO	phenyl)-5-	
	° Y ÇH₃	thiazolecarboxamide	
	N		
-	H <sub>3</sub> C CH <sub>3</sub>	2 [[/2 Mothorn	4 7 7
74	H <sub>3</sub> Q N CH <sub>3</sub>	2-[[(3-Methoxy-phenyl)acetyl]amino]-	4.11
	S CH3	4-methyl-N-(2,4,6-	
	No N	trimethylphenyl)-5-	
	l	thiazolecarboxamide	]
	H₃C CH₃		
75	СН <sub>3</sub> 0-СН <sub>3</sub>	2-[[(3,4-Dimethoxy-	3.90
	O O CH <sub>3</sub>	phenyl)acetyl]amino]-	
	N Ch3	4-methyl-N-(2,4,6-	
	N SLO	trimethylphenyl)-5- thiazolecarboxamide	
	l CH3	Ciliazorecarboxamide	1
	H <sub>3</sub> C CH <sub>3</sub>		
76	a	2-[[(4-Chloro-	4.34
	CH <sub>3</sub>	phenyl)acetyl]amino]-	1.01
	N CLO	4-methyl-N-(2,4,6-	
	CH3	trimethylphenyl)-5- thiazolecarboxamide	
		cirrazorecarboxamide	
Ì	1, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2,		i i
-	H <sub>3</sub> C CH <sub>3</sub>	2-[([1,1'-Biphenyl]-4-	4.00
77	<b>( )</b>	ylacetyl)amino]-4-	4.60
		methy1-N-(2,4,6-	
		trimethylphenyl)-5-	
		thiazolecarboxamide	
	NCH <sub>3</sub>		
	N-(I		777
	S CH₃		
	N.		
1		1	
1			
	н <sub>з</sub> с сн <sub>з</sub>		
78	H <sub>3</sub> C CH <sub>3</sub>	4-Methyl-2-[(1-oxo-4-	4.40
78	N CH <sub>3</sub>	phenylbutyl)amino]-N-	4.40
78	.CH <sub>2</sub>	phenylbutyl)amino]-N- (2,4,6-trimethyl-	4.40
78	N CH <sub>3</sub>	phenylbutyl)amino]-N-	4.40
78	N CH <sub>3</sub>	phenylbutyl)amino]-N- (2,4,6-trimethyl- phenyl)-5-thiazole-	4.40

70			<del></del>
79	N CH3	4-Methyl-2-[(1-	4.65
	5 60 21	oxooctyl)amino]-N- (2,4,6-trimethyl-	
	, the	phenyl)-5-thiazole-	
		carboxamide	
	H <sub>3</sub> C CH		
80	NL CH <sub>3</sub>	2-[(2-Hydroxy-2-	4.13
	CHON	phenyl-1-	1.10
	S CH3	oxopropyl)amino]-4-	
	HO N I''3	methyl-N-(2,4,6-	
	1 Y N	trimethylphenyl)-5-	
	Н₃С СН,	thiazolecarboxamide	
81	A <sub>1</sub> CH <sub>3</sub>		
01	N J GII3	2-[(2-Hydroxy-1- oxohexy1)amino]-4-	4.14
	HQ MS 0	methyl-N-(2,4,6-	}
	J CH₃	trimethylphenyl)-5-	ŀ
	H <sub>3</sub> C	thiazolecarboxamide	
	H <sub>3</sub> C CH <sub>3</sub>		
00			
82	N CH <sub>3</sub>	4-Methyl-2-[[1-oxo-4-	4.32
	Malo	(2-thienyl)- butyl]amino]-N-(2,4,6-	İ
	S-C PH <sub>3</sub>	trimethylphenyl)-5-	
		thiazolecarboxamide	
	l		
	H₃ C CH₃		
83	CH <sub>3</sub> CH <sub>3</sub>	4-Methyl-2-[(3-	4.04
	L N L N L "3	thienylcarbonyl)amino]	
		-N-(2,4,6-trimethyl- phenyl)-5-thiazole-	
	S- O O <sub>H3</sub> C CH3	carboxamide	
84	N CH <sub>3</sub>	2 [/2 ]	
04	, , , , , , , , , , , , , , , , , , ,	2-[(2-Benzofuranyl- carbonyl)amino]-4-	4.37
ł	STAN STAN	methyl-N-(2,4,6-	
	H <sub>1</sub> C CH <sub>2</sub>	trimethylphenyl)-5-	
	H <sub>3</sub> C CH <sub>3</sub>	thiazolecarboxamide	
<u> </u>			
85	CH <sub>3</sub> CH <sub>3</sub>	N-[4-Methyl-5-	3.50
	- N- I N I	[[(2,4,6-trimethyl-	
		phenyl)amino]carbonyl]	1
	OH <sub>3</sub> C CH <sub>3</sub>	-2-thiazolyl]-4- pyridinecarboxamide,	
		pyridinecarboxamide, N-oxide	
		- OATUC	
86	CH <sub>3</sub>	6-Chloro-N-[4-methyl-	4.08
		5-[[(2,4,6-trimethyl-	<b>1.00</b>
	SYYY)	phenyl)amino]carbonyl]	
ł	NE O OHOC CHO	-2-thiazolyl]-3-	I
	<u> </u>	pyridinecarboxamide	i
4			ŀ

		r	
87		N-[4-Methyl-5- [[(2,4,6-trimethyl- phenyl)amino]carbonyl] -2-thiazolyl]-3- pyridinecarboxamide	3.56
88	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N-[4-Methyl-5- [[(2,4,6-trimethyl- phenyl)amino]carbonyl] -2-thiazolyl]-3- quinolinecarboxamide	4.11
89	ON CH3  OCH3  H <sub>3</sub> C  CH3	4-Methyl-2-[[(4- nitrophenyl)acetyl]- amino]-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.08
90	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	4-Methyl-2-[(2,4,6-trichlorobenzoyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.45
91	P CH <sub>3</sub>	4-Methyl-2-[[2-[[3- (trifluoromethyl)- phenyl]amino]benzoyl]- amino]-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.86
92	ON, CH3  H2C CH3	4-Methyl-2-[[4-(4- nitrophenyl)-1- oxobutyl]amino]-N- (2,4,6-trimethyl- phenyl)-5-thiazole- carboxamide	4.28
93	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	4-Methyl-2-[[4- (methyl-sulfonyl)- benzoyl]-amino]-N- (2,4,6-trimethyl- phenyl)-5-thiazole- carboxamide	3.79

0.4	,CH <sub>3</sub>	12 [/A manhallanana]	
94	H3C \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	2-[(4-Heptylbenzoyl) amino]-4-methyl-N-	
1	M CH3	(2,4,6-	
	CH P N	trimethylphenyl)-5-	1
1	N 2 N	thiazolecarboxamide	
}	0=		
1			
	сн		
95	[ Su	2-[[(2,4-Difluoro-	4.15
	N CH <sub>3</sub>	phenyl)acetyl]amino]-	
l	N N LO	4-methyl-N-(2,4,6-	
	F CH <sub>3</sub>	trimethylphenyl)-5- thiazolecarboxamide	]
1	0 1	cirrazorecarboxamide	
1			
<u></u>	H <sub>3</sub> C CH <sub>3</sub>		
96	CH <sub>3</sub> Abs	(S)-2-[[2-	3.20
		(Dipropylamino)-1-	
{		oxopropyl]amino]-4-	
	N CH <sub>3</sub>	methyl-N-(2,4,6- trimethylphenyl)-5-	
	H3C H3CH N	thiazolecarboxamide	
	CH <sub>3</sub>	- Interest of the second secon	
			=
	н <sub>3</sub> с сн <sub>3</sub>		
97	H₃C	2-[(2-Biphenyl-	4.64
	CH <sub>3</sub>	onogarhonis l'aminal 4	7.04
	О № ДУР СН3	methyl-N-(2,4,6-	1
	N'S OH3C	trimethylphenyl)-5-	i 1
		thiazolecarboxamide	1
			1
	<b>V</b>		
98	N CH <sub>3</sub>	2-[[3-(3-	4.26
	N also	Methoxyphenyl)-1-	
	° ° CH3	oxopropyl]amino]-4-	
		methyl-N-(2,4,6- trimethylphenyl)-5-	
	H <sub>3</sub> C-O H <sub>3</sub> C CH <sub>3</sub>	thiazolecarboxamide	
99	H₃Ç	4-Methyl-N-(2,4,6-	4.52
	CH <sub>3</sub>	trimethylphenyl)-2-	1.02
	~3	[[(2,4,6-trimethyl-	
	H <sub>3</sub> C CH	phenyl)acetyl]amino]-	
	CH <sub>3</sub>	5-thiazolecarboxamide	
	N-CI 2		
	° S CH₃		
.	K I I		J
	H <sub>3</sub> C CH <sub>3</sub>		1
			1

100	N CH <sub>3</sub>	4-Methyl-2-[(1-oxo-6-heptenyl)amino]-N-	4.47
	S P CH3	(2,4,6-trimethyl-	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	phenyl)-5-thiazole-	
		carboxamide	
	H₂C H₃C CH₃		
101	(°), CH₃	2-[[(1,3-Benzodioxol-	4.07
		5-y1)acety1]amino]-4- methy1-N-(2,4,6-	
	S CH3	trimethylphenyl)-5-	
		thiazolecarboxamide	
	н₃с Сн₃		
102	N CH3	4-Methyl-2-[[[2-	4.46
	M M LO	(phenylmethoxy)phenyl]	
	o	acetyl]amino]-N- (2,4,6-trimethyl-	
		phenyl)-5-thiazole-	
	H <sub>3</sub> C CH <sub>3</sub>	I	
	·		
103	N-CH <sub>3</sub>	4-Methyl-2-[[(3-	4.56
	Malo	phenoxyphenyl)acetyl]a	
	S T CH <sub>3</sub>	mino]-N-(2,4,6- trimethylphenyl)-5-	
		thiazolecarboxamide	
	H <sub>3</sub> C CH <sub>3</sub>		
104	,O-CH₃	2-[(3,5-Dimethoxy-	4.13
	H <sub>3</sub> C N CH <sub>3</sub>	phenyl)acetyl]amino]-	
	Melo	4-methyl-N-(2,4,6-	
	CH <sub>3</sub>	trimethylphenyl)-5- thiazolecarboxamide	
	" <del> </del>	enrazor coursonament	
	н₃с Сн₃		
105	^a	2-[[4-[4-[Bis(2-	4.75
	∠N N→CHs	chloroethyl)amino]phen	
	a S	yl]-1-oxobutyl]amino]- 4-methyl-N-(2,4,6-	
	, i iii	trimethylphenyl)-5-	
	I I	thiazolecarboxamide	
	H <sub>3</sub> C CH <sub>3</sub>		
106	CH₃	4-[[4-[[[4-methyl-5-	4.03
		[[(2,4,6-trimethyl-phenyl)amino]carbonyl]	
	H <sub>3</sub> C CH <sub>3</sub>	-2-thiazolyl]-amino]-	
}	N Wis	carbonyl]phenyl]-	
	· o s 1 ~	amino]-4-oxobutanoic	
1	N N N	acid methyl ester	
	>		
	o-4		
1	H₃C O		L

	·		
107		4-Methyl-2-[[(phenyl-	3.77
1		sulfonyl)acetyl]amino]	
1	S P CH <sub>3</sub>	-N-(2,4,6-trimethyl-	1
	0 4	phenyl)-5-thiazole-	1
1	N CO	carboxamide	
1	° Y cH₃		1
1	N.		1
1			
	н₃с Сн₃		
108	, CH <sub>3</sub>	2-[[2-(Acetylamino)-1-	3.99
100	H <sub>3</sub> C-\	oxohexyl]amino]-4-	3.99
	- Mayo	methyl-N-(2,4,6-	
	Q → S P CH <sub>3</sub>	trimethylphenyl)-5-	
1	) N O N	thiazolecarboxamide	
	Н₃С [[ ]]		
L	н₃с Сн₃		
109	CH <sub>3</sub>	2-[[4-[(Dipropyl-	4.51
1	H <sub>3</sub> C	amino) sulfonyl]benzoyl	
	V CH3	]amino]-4-methyl-N-	
	CH <sub>3</sub>	(2,4,6-trimethyl-	
1	0 \_(1')	phenyl)-5-thiazole-	
	N	carboxamide	}
1	<b>○</b>		
	SyO /-CH3		
	ري مي المار ال		
j	اسر ا		
<u> </u>	H₃Ć		·
110	,CH₃	2-[(4-Cyclohexyl-	4.94
		benzoyl)amino]-4-	
İ	ا الله ال	methyl-N-(2,4,6-	<b>i</b> [
	H <sub>3</sub> C	trimethylphenyl)-5-	1
	Q N CH <sub>3</sub>	thiazolecarboxamide	
ł	<i>I</i>		
	0 \$ 7		
1	N N		
	N "		
ļ			
	I/Y		
111	,, ,CH <sub>3</sub>	2-[(4-Bromo-3-	1.00
111	N-1 CH3		4.80
	MISHAL	methylbenzoyl)amino]-	
	Br-( ) T T ]	4-methyl-N-(2,4,6-	
	"O ÖH3C CH3	trimethylphenyl)-5-	ŀ
	H <sub>3</sub> C	thiazolecarboxamide	
112	CH <sub>3</sub>	2-[[(2,3-	4.14
	F-( ) N-( )	Difluorophenyl)acetyl]	
		amino]-4-methyl-N-	
	F CH3	(2,4,6-	
	F O N		
		trimethylphenyl)-5-	
	F O H <sub>3</sub> CH <sub>3</sub>		

113	CH <sub>3</sub>	4-Methyl-2-[[[4-(1-	4.56
	H <sub>3</sub> C- N-CH <sub>3</sub> CH <sub>3</sub> N-CH <sub>3</sub>	methylethyl)phenyl]ace tyl]amino]-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	
114	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[[[4-(1,1-Dimethyl-ethyl)cyclohexyl]carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.85
115	H <sub>3</sub> C-N <sub>CH<sub>3</sub></sub> H <sub>3</sub> C CH <sub>3</sub>	N,N-Dimethyl-N'-[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]butanediamide	3.50
116	H <sub>3</sub> C CH <sub>3</sub>	2-[(1,6- Dioxohexyl)amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.40
117	S H <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[(Benzo[b]thiophen- 2-ylcarbonyl)amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.53
118	H <sub>3</sub> C H <sub>3</sub> C H <sub>4</sub> C H <sub>4</sub> C H <sub>4</sub> C H <sub>4</sub> C H <sub>5</sub> C H <sub>5</sub> C H <sub>5</sub> C H <sub>6</sub> C H <sub>7</sub> C	2-[(1-Adamantyl- carbonyl)amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.66

	<del></del>		
119	CH₃	4-Methyl-2-[[(4-	4.48
		methylcyclohexyl)carbo	
1	H <sub>3</sub> C	nyl]amino]-N-(2,4,6-	
	Q CH <sub>3</sub>	trimethylphenyl)-5-	
1	N	thiazolecarboxamide	1
			1
İ	N N		l
	H <sub>3</sub> C		
120	CH <sub>3</sub>	2-[(1,7-Dioxooctyl)-	3.88
	N-(T)	amino]-4-methyl-N-	
	ÇH₃	(2,4,6-trimethyl-	
		phenyl)-5-thiazole-	
1		carboxamide	
	O= H₃C CH₃		1 1
	CH <sub>3</sub>		
121	N 2 CH <sub>3</sub>	2-[[2-(Acetylamino)-4-	3.93
	H <sub>3</sub> C	(ethylthio)-1-	
		oxobutyl]amino]-4-	]
	) ° Y cH₃	methyl-N-(2,4,6- trimethylphenyl)-5-	
	S N	thiazolecarboxamide	
1			
	H <sub>3</sub> C H <sub>3</sub> C CH <sub>3</sub>		
122	N CH₃ CH₃	1,5-Dimethyl-N-[4-	3.91
}	Ha MI NI	methy1-5-[[(2,4,6-	
	Land a Land	trimethylphenyl)amino]	
1	H <sub>3</sub> C <sup>N-N</sup> O H <sub>3</sub> C CH <sub>3</sub>	carbonyl]-2-	İ
		thiazolyl]-1H-	
		pyrazole-3-carboxamide	
123	HQ CH-	2-[[[4-methyl-5-	0.70
123	HO W CH3	[[(2,4,6-	3.70
	N- LO	trimethylphenyl)amino]	
	S CH <sub>3</sub>	carbonyl]-2-	
		thiazolyl]amino]carbon	
	] ]	yl]benzoic acid	
	H₃ C CH₃		
124	CH.	N-[4-Methyl-5-	4.18
	O NOH3C	[[(2,4,6-trimethyl-	<b>1.10</b>
		phenyl)amino]carbonyl]	
	N 3 N CH <sub>3</sub>	-2-thiazolyl]-6-benzo-	. ]
	H <sub>3</sub> C	thiazolecarboxamide	İ
	N s		
125		1-Ethyl-4-methyl-N-[4-	4.00
120		methyl-5-[[ $(2,4,6-$	4.09
		trimethylphenyl)-	1
		amino]carbonyl]-2-	
		thiazolyl]-1H-	1
	3	pyrazole-3-carboxamide	
	[*		]
	<del>"</del>	- <del></del>	

126	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	4-Methyl-2-[[3-[(3H-1,2,3-triazolo[4,5-b]pyridin-3-yloxy)methyl]benzoyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.15
127	S OH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[(2-Furanyl- carbonyl)amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.45
128	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[(4-Chloro- benzoyl)amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	8.85
129	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[(2,2-Dimethyl-1-oxopropyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.30

Example 130

# <u>Preparation of [4-Methyl-5[[(2-nitrophenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester</u>

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2-Nitroaniline (55 mg, 0.4 mmol) and diisopropylethylamine (70  $\mu$ L, 0.4 mmol) were added dropwise to a a stirred solution of 2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid chloride 1C (100 mg, 0.36 mmol) in dichloromethane (3 mL). After 16 h at rt, 4-N,N-dimethylaminopyridine (22 mg, 0.18 mmol) was added and the mixture

was stirred for additional 3.5 h. The solvent was evaporated *in vacuo*. The residue was chromatographed on a silica gel column. Elution with 5% EtOAc in hexanes followed by 20% EtOAc in hexanes afforded the title compound (15 mg, 11%) as a yellow solid.

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#### Example 131

Preparation of [4-Methyl-5[[(2,4,6-trimethylphenyl)amino]carbonyl]-2thiazolyl]carbamic acid, phenylmethyl ester

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A. Ethyl-2-benzyloxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate
A 3 M aq. NaHCO<sub>3</sub> solution (10 mL, 30 mmol) was added to a stirred solution of ethyl-2-amino-4-methyl-thiazole-5-carboxylate (372 mg, 2 mmol) in THF (20 mL) at 0-5°C. Benzyl chloroformate (500 μL) was added.

15 After 2 h, additional benzyl chloroformate (500 μL) and the biphasic solution was stirred for an additional 2 h at 0-5°C. The mixture was diluted with dichloromethane (50 mL) and water (30 mL). The organic layer was separated, dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was chromatographed on a silica gel column. Elution with 10% EtOAc in hexanes followed by 20% and 30% EtOAc in hexanes afforded the title compound (310 mg, 48%) as a white solid.

B. 2-Benzyloxycarbonyloxyamino-4-methyl-thiazole-5-carboxylic acid Compound 131B was prepared by an analogous method as that of 3B, except using 131A to give the title compound 131B as a white powder (77%).

C. [4-Methyl-5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, phenylmethyl ester

Diisopropylethylamine (70 μL, 0.41 mmol) was added to a solution of 131B (100 mg, 0.34 mmol), 2,4,6-trimethylaniline (60 μL, 0.41 mmol), and [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate (HATU, 160 mg, 0.41 mmol). The mixture was stirred at rt for 24 h, diluted with EtOAc (20 mL) and washed with 2 N Aq. HCl solution (3x), brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was triturated with ether (40 mL) to obtain the title compound (100 mg, 77%) as an off-white solid.

#### Example 132

Preparation of Methyl[4-methyl-5-[[(2,4,6-

15 <u>trimethylphenyl)amino|carbonyl|-2-thiazolyl|carbamic acid, 1,1-dimethylethyl ester</u>

Compound 132 was prepared by an analogous method as that of 1, except using ethyl-2-tert-butoxycarbonyloxyaminomethyl-4-methyl-thiazole-5-carboxylate to give the title compound 132 as a tan solid.

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#### Example 133

Preparation of 4-Methyl-2-(methylamino)-N-(2,4,6-trimethylphenyl)-5thiazolecarboxamide, trifluoroacetate (1:1)

Compound 133 was prepared by an analogous method as that of 4, except using 132 to give the title compound 133 as a white solid (91%).

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#### Example 134

#### Preparation of [4-Methyl-5-[[methyl(2,4,6-

#### trimethylphenyl)aminolcarbonyl]-2-thiazolyllcarbamic acid, 1,1-

#### dimethylethyl ester

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Compound 134 was prepared by an analogous method as that of 1, except using N-methyl-2,4,6-trimethylaniline to give the title compound 134 as a white solid (60%).

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#### Example 135

### <u>Preparation of 2-Amino-N,4-dimethyl-N-(2,4,6-trimethylphenyl)-5-</u> thiazolecarboxamide, trifluoroacetate (1:1)

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Compound 135 was prepared by an analogous method as that of 4, except using 134 to give the title compound 135 as a white solid (97%).

#### Example 136

### Preparation of [4-Methyl-5][(2,4,6-trimethylphenyl)aminolcarbonyl]-2thiazolyl]carbamic acid, methyl ester

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A mixture of 2 (100 mg, 0.36 mmol), pyridine (87 μL, 1.08 mmol), methyl chloroformate (111 μL, 1.44 mmol) in dichloromethane (3 mL) was stirred at rt for 1.5 h. The solution was diluted with dichloromethane and washed with aq. NaHCO<sub>3</sub> solution (20 mL, 2x), brine; dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was triturated with ether to obtain the title compound (88 mg, 82%) as a white solid.

#### Example 137

## Preparation of [4-Ethyl-5[[(2,4,6-trimethylphenyl)amino]carbonyl]-2thiazolyl]carbamic acid, 1,1-dimethylethyl ester

Compound 137 was prepared by an analogous method as that of 1, except using methyl-2-amino-4-ethyl-thiazole-5-carboxylate to give the title compound 137 as a white solid (70%).

#### Example 138

### Preparation of 2-Amino-4-ethyl-N-(2,4,6-trimethylphenyl)-5thiazolecarboxamide, trifluoroacetate

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Compound 138 was prepared by an analogous method as that of 4, except using 137 to give the title compound 138 as a white solid (89%).

#### Example 139

### Preparation of [5-[[(2,6-Dichlorophenyl)amino]carbonyl]-4-methyl-2thiazolyl]carbamic acid, 1,1-dimethylethyl ester

A 1 M solution of sodium bis-trimethylsilyl amide (290  $\mu$ L, 0.29 mmol) was added to a stirred solution of 2,6-dichloroaniline (13.4 mg, 0.08 mmol) in THF (1 mL). After 30 min, the mixture was cooled to 0 °C and 1C (30 mg, 0.11 mmol) was added in one portion. The mixture was allowed to warm to rt and stirred for 16 h. The solution was diluted with dichloromethane and washed with 2 N aq. HCl solution (2 mL, 3x), dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 30% EtOAc in hexanes to obtain the title compound (20 mg, 45%) as a light yellow solid.

#### Example 140

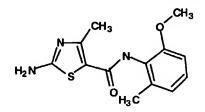
### Preparation of 2-Amino-N-(2,6-dimethylphenyl)-4-methyl-5thiazolecarboxamide, trifluoroacetate (1:1)

5 Compound 140 was prepared by an analogous method as that of 4, except using 53 to give the title compound 140 as a light tan solid (100%).

#### Example 141

Preparation of 2-Amino-N-(2-methoxy-6-methylphenyl)-4-methyl-5-

thiazolecarboxamide, trifluoroacetate (1:1)



Compound 141 was prepared by an analogous method as that of 4, except using 13 to give the title compound 141 as an off-white solid (100%).

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#### Example 142

Preparation of 2-Amino-N-(2-methylphenyl)-4-methyl-5-

thiazolecarboxamide, trifluoroacetate (1:1)

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Compound 142 was prepared by an analogous method as that of 4, except using 18 to give the title compound 142 as a light tan solid (90%).

#### Example 143

## Preparation of 2-Amino-N-(2,6-dimethyl-4-bromophenyl)-4-methyl-5-

thiazolecarboxamide, trifluoroacetate (1:1)

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Compound 143 was prepared by an analogous method as that of 4, except using 15 to give the title compound 143 as a light tan solid (70%).

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#### Example 144

### <u>Preparation of 2-Amino-N-(2-chloro-6-methylphenyl)-4-methyl-5-</u>

thiazolecarboxamide, trifluoroacetate (1:1)

15 Compound 144 was prepared by an analogous method as that of 4, except using 19 to give the title compound 144 as a light tan solid (81%).

#### Example 145

Preparation of 2-Amino-N-(2,4-dimethylphenyl)-4-methyl-5-

thiazolecarboxamide, trifluoroacetate (1:1)

Compound 145 was prepared by an analogous method as that of 4, except using 17 to give the title compound 145 as a light tan solid (68%).

#### Example 146

5 Preparation of 2-Amino-N-(2-methyl-6-isopropylphenyl)-4-methyl-5thiazolecarboxamide, trifluoroacetate (1:1)

Compound 146 was prepared by an analogous method as that of 4, except using 16 to give the title compound 146 as a light tan solid (100%).

#### Example 147

Preparation of 2-(Acetylamino)-4-methyl-N-(2,4,6-trimethylphenyl)-5-

#### thiazolecarboxamide

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A mixture of 2 (54 mg, 0.2 mmol), acetic anhydride (22 µL, 0.23 mmol), dimethylaminopyridine (3 mg) in dichloromethane (4.5 mL) was stirred at rt for 4.5 h. The mixture was diluted with dichloromethane (65 mL) and washed with 1 N aq. HCl solution (20 mL), water; dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 35% EtOAc in hexanes to obtain the title compound (43 mg, 69%) as a white solid.

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#### Example 148

## <u>Preparation of 2-(Benzoylamino)-4-methyl-N-(2,4,6-trimethylphenyl)-5-</u> <u>thiazolecarboxamide</u>

A solution of 2 (100 mg, 0.36 mmol) and benzoic anhydride (226 mg, 1 mmol) in dichloromethane (10 mL) and pyridine (2 mL) was stirred at rt overnight. The mixture was diluted with dichloromethane (50 mL) and washed with 2 N aq. HCl solution (15 mL, 2x), 10% aq. NaHCO<sub>3</sub> solution (20 mL, 2x); dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 30% EtOAc in hexanes followed by 50% EtOAc in hexanes to obtain the title compound contaminated with benzoic acid. The solid was dissolved in EtOAc (40 mL) and washed with satd. KHCO<sub>3</sub> solution (15 mL, 4x), dried (MgSO<sub>4</sub>), filtered and concentrated to obtain the title compound (110 mg, 80%) as a white solid.

#### Example 149

# <u>Preparation of 4-methyl-2-[(1-oxopropyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide</u>

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A mixture of 2 (100 mg, 0.36 mmol), propionic anhydride (332  $\mu$ L, 2.58 mmol) in dichloromethane (10 mL) and pyridine (4 mL) was stirred at rt for 3 h. Dimethylaminopyridine (122 mg, 1 mmol) was added and the mixture was stirred for additional 1.5 h. The mixture was diluted with dichloromethane and washed with 1 N aq. HCl solution (25 mL, 3x), aq.

NaHCO3 solution (20 mL, 2x), water(20 mL), brine; dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 20% EtOAc in hexanes to obtain the title compound (81 mg, 68%) as a white solid.

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#### Example 150

## <u>Preparation of 4-methyl-2-[(1-oxobutyll)aminol-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide</u>

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Compound 150 was prepared by an analogous method as that of 149, except using butyric anhydride to give the title compound 150 as a white solid (76%).

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#### Example 151

## <u>Preparation of 4-methyl-2-[(1-oxopentyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide</u>

Compound 151 was prepared by an analogous method as that of 149, except using valeric anhydride to give the title compound 151 as a white solid (77%).

#### Example 152

## <u>Preparation of 4-methyl-2-[(1-oxohexyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide</u>

5 Compound 152 was prepared by an analogous method as that of 149, except using hexanoic anhydride to give the title compound 152 as a white solid (75%).

#### Example 153

## 10 <u>Preparation of 4-Methyl-2-[(phenylcetyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide</u>

A solution of amine 2 (50 mg, 0.18 mmol), diisopropylethylamine (101 μL, 0.58 mmol), phenylacetic acid (27.2 mg, 0.20 mmol), 1-hydroxy-7-azabenzotriazole (29.4 mg, 0.22 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (42.2 mg, 0.22 mmol) in dichloromethane (0.62 mL) was mechanically stirred in a sealed vial for 16 h. The reaction mixture was passed through a Varian SCX ion exchange column (2 g/6 cc) and eluted with acetonitrile-methanol (10 mL, 4:1) followed by 2 M methanolic ammonia solution (9 mL). Fractions containing the product were combined and then concentrated. The residue was dissolved in dichloromethane and washed with 2 N aq. HCl solution (3x), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to obtain the title compound 25 (39 mg, 55%) as a tan solid.

#### Example 154

## Preparation of 2-[[(Acetylamino)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-6-thiazolecarboxamide

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A solution of amine 2 (50 mg, 0.18 mmol), diisopropylethylamine (400 μL, 2.3 mmol), N-acetylglycine (42 mg, 0.36 mmol), 1-hydroxy-7-azabenzotriazole (49 mg, 0.36 mmol), and ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (72 mg, 0.36 mmol) in THF (5 mL) was heated to 50°C overnight. The mixture was cooled, diluted with dichloromethane (60 mL) and washed with 2 N aq. HCl solution (20 mL), satd. aq. KHCO<sub>3</sub> solution (20 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. The crude solid was triturated with ether (10 mL), filtered, and washed with ether (5 mL, 3x) to obtain the title compound (40 mg, 59%) as an off-white solid.

#### Example 155

### <u>Preparation of 2-Amino-4-methyl-N-(2,4,6-trimethylphenyl)-5-</u> thiazolecarbothioamide

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A suspension of 2 (50 mg, 0.18 mmol) and Lawesson reagent (44 mg, 0.11 mmol) in toluene (0.23 mL) was heated to 100°C for 4h. Additional Lawesson reagent (44 mg, 0.11 mmol) was added and the mixture was heated for additional 3.5 h. The crude mixture was chromatographed on a

silica gel column and eluted with 50% EtOAc in hexanes followed by 70% EtOAc in hexanes to obtain a a yellow solid which was triturated with hexanes (6 mL) to obtain the title compound (11 mg, 21%) as a yellow solid.

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#### **Examples 156 to 170**

#### General Procedure

Compounds 156 to 170 were prepared following the procedure described below. Diisopropylethyl amine (60 µL, 0.34 mmol) was added to a mixture of amine 2 (30 mg, 0.11 mmol), appropriate carboxylic acid (0.13 mmol), 1hydroxy-7-azabenzotriazole (19.5 mg, 0.14 mmol), and ethyl-3-(3dimethylamino)-propyl carbodiimide hydrochloride (26.8 mg, 0.14 mmol) in THF (1 mL). The mixture was heated in a sealed tube under argon at 45  $^{\circ}\mathrm{C}$  for 24 h. The reaction mixture was diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (2 mL, 3x), dried (Na2SO4) and concentrated using a speedvac. The crude products were either triturated with dichloromethane-ether (5 mL, 1:1) or purified by silica gel chromatography (elution solvent: 50% EtOAC in hexanes and EtOAc). "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10%  $H_2O,\,0.2\%$   $H_3PO_4),$  flow rate 4 mL/min,  $\lambda$ = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
156		2-[(4- Bromobenzoyl)amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	5.03

457	,CH <sub>3</sub>	4-Methyl-2-[(4-	4.07
157	Ö N—1, ∠,,3 CH³	nitrobenzoyl)amino]-N-	4.87
	CAN N'S N'	(2,4,6-	
	in the second se	trimethylphenyl)-5-	
		thiazolecarboxamide	
158	O M CH3	2-[(4-	4.70
		Cyanobenzoyl)amino]-4-	
		methyl-N-(2,4,6- trimethylphenyl)-5-	
	F <sub>3</sub> C CH <sub>3</sub>	thiazolecarboxamide	ŀ
159	CH <sub>3</sub>	4-Methyl-2-[[(5-nitro-	4.63
		2-	
1	N S J J	furanyl)carbonyl]amino	
1	N <sub>3</sub> c CH <sub>3</sub>	]-N-(2,4,6- trimethylphenyl)-5-	
	0 NF	thiazolecarboxamide	
	<b>.</b>		
160	CH <sub>3</sub>	4-Methyl-2-[(2-	4.60
		thienylcarbonyl)amino]	
	N S T T	-N-(2,4,6-	
	l <sup>™</sup> s P <sub>3</sub> c CH <sub>3</sub>	trimethylphenyl)-5- thiazolecarboxamide	
		Chiazorecarboxamide	
161	CH <sub>3</sub>	4-[[[4-Methyl-5-	4.99
		[[(2,4,6-	1.00
	all wall	trimethylphenyl)amino]	
1	H³C A CH³	carbonyl]-2- thiazolyl]amino]carbon	
		yl]benzoic acid methyl	
		ester	
162	O N-1 CH3	2-[(5-	4.87
	LILLNI"	Isoxazolylcarbonyl)ami	
	T N S T T ]	no]-4-methyl-N-(2,4,6- trimethylphenyl)-5-	
	H <sub>3</sub> C CH <sub>3</sub>	thiazolecarboxamide	
163	CH <sub>3</sub>		4.54
		amino]-4-methyl-N-	
	M s J "	(2,4,6-	
	°O <sup>-1</sup> β <sub>3</sub> C <sup>-1</sup> CH <sub>3</sub>	trimethylphenyl)-5- thiazolecarboxamide	
	•	CHITAZOI GCAI DONAIRIAG	
164	,CH₃	2-[[(2,4-Dimethyl-5-	4.74
	H <sub>3</sub> ¢ P N	thiazolyl)carbonyl]ami	
	N S N S	no]-4-methyl-N-(2,4,6-	
	β <sub>3</sub> c CH <sub>3</sub>	trimethylphenyl)-5-	
	H₃C	thiazolecarboxamide	

100	CI.		
165	H <sub>3</sub> C-O O N S H <sub>3</sub> C CH <sub>3</sub>	2-[[(4-Methoxy-3-thienyl)carbonyl]amino ]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.75
166	O H S CH3  CH3  CH3	4-Methyl-2-[[(5-nitro-3-thienyl)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	
167	S P CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[[4-[(4- Chlorophenyl)thio]-3- thienyl]carbonyl]amino ]-4-methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	5.27
168	H <sub>3</sub> C-O O N S CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[[(5-Chloro-4-methoxy-3-thienyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.04
169	N CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[[[2-(4,5-Dihydro- 4,4-dimethyl-2- oxazolyl)-3- thienyl]carbonyl]amino ]-4-methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	5.13
170	S CHA B CH	2-[[(2-Acetyl-3- thienyl)carbonyl]amino ]-4-methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.54

## Examples 171 to 180

### General Procedure

Compounds 171 to 180 were prepared following the procedure described

5 below.

A mixture of 2 (80 mg, 0.29 mmol), appropriate isocyanate (0.87 mmol) and pyridine (2 mL) in THF (3.5 mL) was stirred at rt overnight. In some cases the reaction mixture was heated to 60-70°C for 5 h. Some of these reactions were carried out at rt overnight in the presence of catalytic N,Ndimethylaminopyridine. The reaction mixture was diluted with dichloromethane and washed with 1 N aq. HCl solution (3x), water, brine; dried (MgSO<sub>4</sub>), filtered and concentrated. The crude product was purified either by trituration with ether or ether-hexanes mixture, or by chromatography on a silica gel column (elution solvent 20-40% EtOAc in hexanes) followed by trituration or by passing through Varian cation exchange SCX cartridge and sequentially eluted with methanol (5 mL), dichloromethane (5 mL), acetonitrile-methanol (10 mL, 4:1) and methanol-2 M methanolic ammonia (10 mL, 4:1) to obtain the title compound. "HPLC Ret Time" is the HPLC retention time under the following conditions: For compounds 171-172, 175, and 177 HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short column, 30 min gradient starting from 100% solvent A (10% MeOH, 90% H2O, 0.2% H2PO, ) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 2.5 mL/min,  $\lambda = 217$  nM. For the other compounds HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short column, 8 min gradient starting from 100% solvent A (10% MeOH, 90%  $H_2O$ , 0.2%  $H_3PO_4$ ) to 100% solvent B (90% MeOH, 10%  $H_2O$ , 0.2% H<sub>2</sub>PO<sub>4</sub>), flow rate 2.5 mL/min,  $\lambda = 217$  nM.

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EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
171	H <sub>3</sub> C N N S H <sub>3</sub> C CH <sub>3</sub>	4-Methyl-2-[[(methyl-amino)carbonyl]amino]- N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	24.48

172	N CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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173	H <sub>3</sub> C-CH <sub>3</sub> H <sub>3</sub> C CH	4-Methyl-2-[[[(4-methylphenyl)amino]-carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.81
174	CH <sub>3</sub> H <sub>3</sub> C  H <sub>3</sub> C  CH	4-Methyl-2-[[[(phenyl-methyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.52
175	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[[(Butylamino) carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	30.49
176	H <sub>3</sub> C N N S H <sub>3</sub> C CH <sub>3</sub>	4-Methyl-2- [[(propylamino)carbony l]amino]-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	7.41
177	N S H <sub>3</sub> C CH;	2-[[(Cyclohexylamino) carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	27.21
178	CH.	2-[[[(2-Chloro- phenyl)amino]carbonyl] amino]-4-methyl-N- (2,4,6-trimethyl- phenyl)-5-thiazole- carboxamide	8.99
179	N N S H <sub>3</sub> C CH	2-[[[(3-Fluorophenyl) amino]carbonyl]amino]- 4-methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	8.87

#### Example 181

## Preparation of [5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, phenyl ester

5

A 10% aq. KHCO<sub>3</sub> solution (170 mL) was added to a stirred solution of 2 (1.02 g, 3.7 mmol) in THF (130 mL). Phenylchloroformate (1.39 mL, 11.1 mmol) was added dropwise. The biphasic mixture was stirred at rt overnight, diluted with dichloromethane (200 mL) and washed with water (50 mL, 2x) and brine. The organic extract was separated, dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 10% EtOAc in hexanes to obtain the title compound (980 mg, 69%) as a solid.

15

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#### Examples 182 to 236

#### General Procedure

Compounds 182 to 236 were prepared following the procedure described below.

A solution of phenylcarbamate 181 (20 mg, 0.054 mmol) and the appropriate amine (0.08 mmol) in THF-acetonitrile (3 mL, 1:1) was stirred at rt overnight. Some of the reactions required heating to 60 °C for 4 h to overnight. The mixture was diluted with dichloromethane (4 mL) and washed with 1 N aq. HCl solution (1.5 mL, 2x), 1 N aq. NaOH solution

(1.5 mL, 2x). The dichloromethane extract was separated, dried (MgSO $_4$ ), filtered and concentrated to obtain the title product.

"HPLC Ret Time" is the HPLC retention time under the following conditions: For compounds 182-192 HPLC conditions are: Zorbax SB-C18

4.5 mm x 7.5 cm short column, 8 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 2.5 mL/min, λ = 217 nM. For compounds 193-236 HPLC conditions are: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 4 mL/min, λ = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
182	N N S H <sub>3</sub> C CH <sub>3</sub>	4-Methyl-2-[[[(2-phenylethyl)amino]-carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.83
183	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	2-[[(Hexylamino) carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	9.01
184	H <sub>3</sub> C CH <sub>3</sub> 0 N CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	2-[[[(1,1-Dimethyl-ethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	8.48
185	CH <sub>3</sub>	2-[[[(3-Fluoro-4- methylphenyl)amino]- carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	8.92

186	H <sub>3</sub> C <sub>0</sub> N N S N <sub>3</sub> C CH <sub>3</sub>	2-[[[(4-Methoxyphenyl) amino]carbonyl]amino]- 4-methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	8.57
187	H <sub>3</sub> C N S H <sub>3</sub> C CH <sub>3</sub>	2-[[(Diethylamino) carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	8.19
188	H <sub>3</sub> C O N CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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189	CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	4-Methyl-2-[[[methyl- (phenylmethyl)amino]- carbonyl]amino]-N- (2,4,6-trimethyl- phenyl)-5-thiazole- carboxamide	8.56
190	CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	4-Methyl-2-[[(methyl-phenylamino)carbonyl]a mino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.39
191	CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	2-[[(Cyclohexylmethyl amino)carbonyl]amino]- 4-methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	8.84
192	CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	4-Methyl-2-[[[(1- phenylethyl)amino]- carbonyl]amino]-N- (2,4,6-trimethyl- phenyl)-5-thiazole- carboxamide	8.47
193	H <sub>3</sub> C CH <sub>3</sub>	2-[[[(Cyclopropyl- methyl) propylamino]- carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.36

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194	CH <sub>3</sub>	4-Methyl-2-[[[(2-	4.42
	<u>                                     </u>	methylcyclohexyl)amino	
1	N ,CH <sub>3</sub>	]carbonyl]amino]-N-	1
1	0=	(2,4,6-trimethyl-	
	N S O S	phenyl)-5-thiazole-	1
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	N-CT	carboxamide	
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		trimethylphenyl)-5-	
İ	н₃с СС СН₃	thiazolecarboxamide	
	.35		
197		2-[[[(2,3-Dihydro-1H-	4.35
		inden-1-yl)amino]	
	N , CH <sub>3</sub>	carbonyl]amino]-4-	
1		methyl-N-(2,4,6-	
	" \s \ CH3	trimethylphenyl)-5-	
1	N Ins	thiazolecarboxamide	
	H₃ C CH₃		
198	M CH <sub>3</sub>	4-Methyl-2-[[[(1-	4.42
.~~	, , , , , , , , , , , , , , , , , , ,	naphthalenylmethyl)ami	4.43
	( ) N s	no]carbonyl]amino]-N-	ĺ
	N-N CH <sub>3</sub>	(2,4,6-trimethyl-	
		phenyl)-5-thiazole-	
		carboxamide	
	H₃ C CH₃		
199		2-[[Bis(phenylmethyl)	4.66
	CH <sub>3</sub>	amino]carbonyl]amino]-	±.00
		4-methyl-N-(2,4,6-	
	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	trimethylphenyl)-5-	
	S T CH <sub>3</sub>	thiazolecarboxamide	Į
			ľ
	H₃C CH₃		1
	1130 0113		

		10 0 0 1 1 1 2 2 2 2 2	1
200	H <sub>3</sub> C OH <sub>3</sub> C OH <sub>3</sub> C	2,6-Dimethyl-N-[4-methyl-5-[[(2,4,6-trimethylphenyl)-amino]carbonyl]-2-thiazolyl]-4-morpholinecarboxamide	3.97
	CH <sub>3</sub>		
201	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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202	CH <sub>3</sub> CH <sub>3</sub> C N S N CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	1-[[4-Methyl-5- [[(2,4,6-trimethyl- phenyl)amino]carbonyl] -2-thiazolyl]- amino]carbonyl]-3- piperidinecarboxylic acid ethyl ester	4.10
203	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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204	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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205	CH <sub>3</sub> O N CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	4-Methyl-2-[[[(3-methyl-2-pyridinyl)-amino] carbonyl]-amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazolecarboxamide	3.51

[	T		
206		4-Methyl-2-[[[1-	3.28
i		<pre>(phenylmethyl)-4- piperidinyl]amino]-</pre>	
	N CH2	carbonyl]amino]-N-	
1		(2,4,6-trimethyl-	
-	N S O	phenyl)-5-thiazole-	
	J CH₃	carboxamide	
	N N		
1		·	
225	H₃C CH₃		
207	CH <sub>3</sub>	Octahydro-N-[4-methyl-	4.55
	o N Atsc	5-[[(2,4,6-trimethyl-	
	N N S N CH <sub>3</sub>	phenyl)amino]carbonyl]	
İ	N II - III	-2-thiazolyl]-1(2H)-	
1	H₃Ć	quinolinecarboxamide	
208	CH <sub>3</sub>	3,4-Dihydro-N-[4-	4.05
200		methyl-5-[[(2,4,6-	4.35
	~ // 🦻	trimethylphenyl)-	1
	H3C >	amino] carbony1]-2-	
	O / CH <sub>3</sub>	thiazolyl]-2(1H)-	
	$I^{"}$	isoquinoline	İ
	ρ Ş <sup>™</sup> CH₃	carboxamide	
	~~~~~~		
	<b>~~</b>		
209	N CH <sub>3</sub>	2-[[[(1,5-Dimethyl-	4.72
	N-Pello	hexyl)amino]carbonyl]-	
-	N-( s ) CH3	amino]-4-methyl-N-	
	CH <sub>3</sub>	(2,4,6-trimethyl-	
	H <sub>3</sub> C CH <sub>3</sub>	phenyl)-5-thiazole-	
	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	carboxamide	
210	NL ∠CH3	4-Mothyl 2 [[[]	
210		4-Methyl-2-[[[(1-	4.74
]	N S PO AU	methylheptyl)amino]-	ļ
	N CH3	carbonyl]amino]-N-	
	CH <sub>3</sub>	(2,4,6-trimethyl-	ļ
1	H <sub>3</sub> C CH <sub>3</sub>	phenyl)-5-thiazole- carboxamide	
	H <sub>3</sub> Ć	carboyamide	
211	N CH₃	2-[[[[(2-Fluoro-	4 177
[-'']		phenyl)methyl]amino]-	4.17
	/' \c\\\ \\	carbonyl]amino]-4-	I
	N CH <sub>3</sub>	methyl-N- $(2,4,6-$	ļ
		trimethylphenyl)-5-	
		thiazolecarboxamide	!
[ i	H <sub>3</sub> C CH <sub>3</sub>		ĺ
1			

212	H <sub>3</sub> C	2-[[[(2-Methoxy-phenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(2-Ethoxy-phenyl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-	4.22
214	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub></sub>	thiazolecarboxamide  2-[[[(3-Methoxy- phenyl)methyl]amino]- carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.13
215	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[[[(4-Chloro- phenyl)methyl]amino]- carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.36
216	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	2-[[[(4-Methoxy-phenyl)methyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.12
217	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[[(2,2-Diphenyl-ethyl)amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.57
218	H <sub>2</sub> N CH <sub>3</sub> CH <sub>3</sub>	2-[[[(2-Aminoethyl) phenylamino]carbonyl]- amino]-4-methyl-N- (2,4,6-trimethyl- phenyl)-5-thiazole- carboxamide	3.70

219	Chi Sho CH3	2-[[[[2-(3-Methoxy-phenyl)ethyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.26
220	CH <sub>3</sub> O-CH <sub>3</sub> CH <sub>3</sub>	2-[[[2-(3,4-Dimethoxyphenyl)ethyl]amino]carbonyl]amino]-	4.05
	H <sub>3</sub> C CH <sub>3</sub>	4-methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	
221	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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222	H <sub>3</sub> C CH <sub>3</sub>	4-Methyl-2-[[[(3-phenylpropyl)amino]-carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.40
223	H <sub>3</sub> C CH <sub>3</sub>	2-[[[[2-(Cyclohex-1-en-1-yl)ethyl]-amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.11
224	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> O=N CH <sub>3</sub> O CH <sub>3</sub> N CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[[[4-(1,1-Dimethylethyl)cyclo-hexyl]amino]carbonyl]-amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.85
225	H <sub>3</sub> C CH <sub>3</sub>	2-[[[(3-Butoxypropyl) amino]carbonyl]amino]- 4-methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.33

226	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[[[2-(2-Methoxy-phenyl)ethyl]amino]-carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.46
227	FCH <sub>3</sub> O  H <sub>3</sub> C  CH <sub>3</sub>		4.39
228	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	2-[[(Hexylmethylamino) carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.65
229	Ch <sub>3</sub>	2-[[[1-(4-Chloro- phenyl)ethyl]amino]- carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	4.42
230	CH3  N CH3  N CH3  N CH3  H <sub>3</sub> C CH3	2-[[[2-(3-Chloro-phenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.44
231	S N S CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	4-Methyl-2-[[[[2-(2-thienyl)ethyl]amino]-carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.18
232	F CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[[[[2-(2-Fluoro- phenyl)ethyl]amino]- carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	5.85
233	N CH <sub>3</sub>	4-Methyl-2-[[[[2-(2-pyridinyloxy)ethyl]-amino]carbonyl]amino]-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.28

234	H <sub>3</sub> C, CH <sub>3</sub> H <sub>3</sub> C, N S CH <sub>3</sub> H <sub>3</sub> C, CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	2-[[[(2-Bromo-4,5-dimethoxyphenyl)methyl]methylamino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	3.87
235	H <sub>3</sub> CC CH <sub>3</sub>	(E)-2-[[[(3,7-Dimethyl-2,6-octa-dienyl) amino]-car-bonyl]amino]-4-methyl-N-(2,4,6-trimethyl-phenyl)-5-thiazole-carboxamide	4.34
236		2-[[[(2,3-Dihydro- 1,4-benzodioxin-2- yl)methyl]amino]car- bonyl]amino]-4-methyl- N-(2,4,6-trimethyl- phenyl)-5-thiazole- carboxamide	4.27

### Examples 237 to 285

#### General Procedure

Compounds 237to 285 were prepared following the procedure described

5 below.

A solution of phenylcarbamate 181 (20 mg, 0.054 mmol) and the appropriate amine (0.08 mmol) in THF-acetonitrile (3 mL, 1:1) was stirred at rt overnight. The mixture was diluted with dichloromethane (4 mL) and washed with 1 N aq. HCl solution (1.5 mL, 2x), 1 N aq. NaOH solution (1.5 mL, 2x). The dichloromethane extract was separated, dried (MgSO<sub>4</sub>), filtered and concentrated to obtain the title product.

"HPLC Ret Time" is the HPLC retention time under the following conditions: For compounds 237-278 HPLC conditions are: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.2% H<sub>3</sub>PO<sub>4</sub>), flow rate 4 mL/min, λ = 220 nM. For compounds 279-285 HPLC conditions are: Zorbax S8-C18 4.5 mm x 7.5 cm short

column, 8 min gradient starting from 100% solvent A (10% MeOH, 90%  $H_2O$ , 0.2%  $H_3PO_4$ ) to 100% solvent B (90% MeOH, 10%  $H_2O$ , 0.2%  $H_3PO_4$ ), flow rate 2.5 mL/min,  $\lambda$  = 217 nM.

EX.	Compound Structure	Compound Name	HPLC
NO.	Compound Structure	Compound Name	Ret
' ' '			Time
			(min)
237	s F	2-[[[[3-Methoxy-5-	5.36
	'≯ <sub>F</sub>	(trifluoromethyl)phenyl]	
}	H₃ Ç	amino]carbonyl]amino]-4-	
		methyl-N-(2,4,6- trimethylphenyl)-5-	
	N N CH₃	thiazolecarboxamide	
	N-VIII		
	S T CH₃		
	H <sub>3</sub> C CH <sub>3</sub>		
238		2-[[[(4-Cyclohexyl-	4.73
	· ·	phenyl) amino]carbonyl]-	
		amino]-4-methyl-N-	
		(2,4,6-trimethylphenyl)- 5-thiazolecarboxamide	
	N , CH <sub>3</sub>		
	s P CH3		
	N. J.	• •	
1			
	H₃ C CH₃		
239		4-Methyl-2-[[[(5,6,7,8-	5.38
		tetrahydro-1- naphthalenyl)amino]-	
		carbonyljamino]-N-	
	N N CH₃	(2,4,6-trimethylphenyl)-	
	OF NOT	5-thiazolecarboxamide	
	" `ѕ С С С С С С С С С С С С С С С С С С		
	N.		
	H <sub>3</sub> C CH <sub>3</sub>		

-	T		<del>,</del>
240	R	2-[[(1-Anthracenylamino) carbonyl]amino]-4-	4.82
		methyl-N-(2,4,6-	
	ï	trimethylphenyl)-5-	1.
	s_n	thiazolecarboxamide	
1	H <sub>3</sub> C N CH <sub>3</sub>		
	)"³ <b>)</b> _( "°	ľ	
	(		l
	)		
044	H₃C		
241	a	2-[[[(4-Chloro-1-	4.76
1		naphthalenyl)amino]- carbonyl]amino]-4-	
İ		methyl-N-(2,4,6-	
ĺ	N , CH <sub>3</sub>	trimethylphenyl)-5-	
		thiazolecarboxamide	İ
	s o au		
	CH <sub>3</sub>		
	"		
	H₃C CH₃		
242	1,30 0,13	4-Methyl-2-[[(2-	r 00
242		naphthalenylamino) -	5.28
]		carbonyl]amino]-N-	
1	N au	(2,4,6-trimethylphenyl)-	
	N N CH₃	5-thiazolecarboxamide	
1	N- N-		
	S Y CH₃		
0.40	H <sub>3</sub> C CH <sub>3</sub>	0.6641777777	
243	o A	2-[[(1H-Indol-5-	5.00
		ylamino)carbonyl]amino]- 4-methyl-N-(2,4,6-	
	N N	trimethylphenyl)-5-	
1	s <sup>∕</sup> N	thiazolecarboxamide	
	)=(		
l i	H₃Ç ,N—( CH₃		
	<b>&gt;</b> ≒ °		İ
	<b>√</b> _СН₃		
	нзс		
244	_Q	2-[[(1,3-Benzodioxol-5-	4.76
		ylamino)carbonyl]amino]-	4.70
		4-methyl-N-(2,4,6-	
	N ., CH <sub>3</sub>	trimethylphenyl)-5-	
		thiazolecarboxamide	1
	N-( LO		
	s		ľ
	u		
	H₃ C CH₃		

	<del>,</del>	1	т—
245	/=N	4-Methyl-2-[[(2-pyra-	3.84
	<b>\</b>	zinylamino)carbonyl]amin	
	N-1	o]-N-(2,4,6-trimethyl-	
	<sub>→</sub> N <sub>N →</sub> CH <sub>3</sub>	phenyl)-5-thiazole-	i
		carboxamide	
	S O		
1	l gH³		
		_	
	н₃с Сн₃		
246	CL	2-[[[(5-Chloro-2-	4.00
240	(m)		4.38
		pyridinyl)amino]carbonyl	
İ		]amino]-4-methyl-N-	
	,N CH	(2,4,6-trimethylphenyl)-	
	CH <sub>3</sub>	5-thiazolecarboxamide	
	\ \\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\		
	S Y CH₃		ŀ
1	h I''		
1			
1			1
	H₃C CH₃		<u> </u>
247		4-Methyl-2-[[[(6-methyl-	4.44
	H <sub>3</sub> C-\(\)	2-pyridinyl) amino]-	
	N-\	carbonyl]amino]-N-	1
	/NCH₃	(2,4,6-trimethylphenyl)-	
		5-thiazolecarboxamide	
	" `s" o		
	S Y CH <sub>3</sub>		
	<b>N</b>		
		·	
	H <sub>3</sub> C CH <sub>3</sub>		
248	F	4-Methyl-2-[[[(2-methyl-	5.23
	N=⟨ //	4-quinolinyl)amino]	
	H <sub>3</sub> C-( )	carbonyl]amino]-N-	
]	130	(2,4,6-trimethylphenyl)-	
	N ,CH <sub>2</sub>	5-thiazolecarboxamide	
		2 CHIGEOTECAL DOVUMITOR	
	NY CLO		
	S CH <sub>3</sub>		
	N. J.		
	Y "		
	H₃C CH₃		
040	-0	2 [[[/2 2 Dib 1 4	1.70
249	<u></u>	2-[[[(2,3-Dihydro-1,4-	4.72
	\)	benzodioxin-6-	
		yl)amino]carbonyl]amino]	
	N , CH <sub>3</sub>	-4-methyl-N-(2,4,6-	
[	My Cri3	trimethylphenyl)-5-	
	`N-( ) _0	thiazolecarboxamide	
	S ÇH₃		
	N I		
	" <b>\</b>		
	H <sub>3</sub> C CH <sub>3</sub>		

	1		
250	00	2-[[([1,1'-Biphenyl]-2-ylamino)carbonyl]amino]- 4-methyl-N-(2,4,6-	5.29
	N CH <sub>3</sub>	trimethylphenyl)-5-	
	N N N	thiazolecarboxamide	
	l s l ch₃		
	H <sub>3</sub> C CH <sub>3</sub>		
251	н₃с- Q	2-[[[(4-Methoxy-2-	4.80
	CH₃	methylphenyl)amino]car-	
		bonyl]amino]-4-methyl-N- (2,4,6-trimethylphenyl)-	
	N, CH <sub>3</sub>	5-thiazolecarboxamide	
	N-CO		
	° r cH₃		
			ļ
	н₃с СН₃		
252	H₃C	4-Methyl-N-(2,4,6-	5.06
	CH₃	trimethylphenyl)-2- [[[(2,4,6-	
		[trimethylphenyl)amino]-	
	H <sub>3</sub> C N CH <sub>3</sub>	carbonyl]amino]-5-	
	N O	thiazolecarboxamide	
	° T pH₃		
	н₃с Сн₃		
253		2-[[[[2-(2-Hydroxy-	4.02
	Ущ∕ Чон	ethyl)phenyl]amino]car- bonyl]amino]-4-methyl-N-	
	N CH <sub>3</sub>	(2,4,6-trimethylphenyl)-	,
	N C L CO	5-thiazolecarboxamide	
	s Y cH₃		
	N		
	H₃ C CH₃		
254	H <sub>3</sub> Ç	2-[[[(3-Methoxyphenyl)	4.86
		amino]carbonyl]amino]-4-	
	N CH <sub>3</sub>	methyl-N-(2,4,6- trimethylphenyl)-5-	
	N-VII	thiazolecarboxamide	
	°S CH₃		
	<b>N</b>		
	н <sub>з</sub> с сн <sub>з</sub>	İ	
LL	.,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		

| 2-[[[(4-Methoxy[1,1'-biphenyl]-3-yl) amino] carbonyl] - amino] -4-methyl-N-(2,4,6-trimethylphenyl) -5-thiazolecarboxamide  2-[[[(3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl) -5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl) -5-thiazolecarboxamide  4.12  And CH3  CH3  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl) -5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl) phenyl] amino]carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl) -5-thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         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trimethylphenyl)-5- trimethylphenyl)-5- trimethyl-N-(2,4,6- trimethylphenyl)-5-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          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(2,4,6-trimethylphenyl)- 5-thiazolecarboxamide  2-[[[(3-Acetylphenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[((4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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5-thiazolecarboxamide  2-[[[(3-Acetylphenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[(4-Fluoro-2- (trifluoromethyl)phenyl]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  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                                           | biphenyl]-3- yl) amino] carbonyl]- amino]-4-methyl-N- (2,4,6-trimethylphenyl)- 5-thiazolecarboxamide  256  H <sub>3</sub> C  CH <sub>3</sub> CH <sub>3</sub> 2-[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[([4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[([4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide                                                                                                                                                                                                                         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trimethylphenyl)-5- thiazolecarboxamide  2-[[([4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[([4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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amino]carbonyl]amino]-4- methyl-N-(2,4,6-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                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amino] -4- methyl-N-(2,4,6- trimethylphenyl) -5- thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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2-[[[(3-Acetylphenyl) amino] carbonyl] amino] -4- methyl-N-(2,4,6- trimethylphenyl) -5- thiazolecarboxamide  2-[[(4-Cyanophenyl) amino] carbonyl] amino] -4- methyl-N-(2,4,6- trimethylphenyl) -5- thiazolecarboxamide  2-[[(4-Cyanophenyl) amino] carbonyl] amino] -4- methyl-N-(2,4,6- trimethylphenyl) -5- thiazolecarboxamide  2-[[[[4-Fluoro-2- (trifluoromethyl) phenyl]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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                         | yl) amino]carbonyl]- amino]-4-methyl-N- (2,4,6-trimethylphenyl)- 5-thiazolecarboxamide  2-[[[(3-Acetylphenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[((4-Hexyloxyphenyl)) 4.42                                                                                                                                                                                                                                                                                                                                                                                                             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amino] -4-methyl-N- (2,4,6-trimethylphenyl) -5-thiazolecarboxamide  2-[[[(4-Cyanophenyl) amino] carbonyl] amino] -4- methyl-N-(2,4,6- trimethylphenyl) -5- thiazolecarboxamide  2-[[[(4-Cyanophenyl) amino] carbonyl] amino] -4- methyl-N-(2,4,6- trimethylphenyl) -5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl) phenyl] amino] carbonyl] amino] -4- methyl-N-(2,4,6- trimethylphenyl) -5- thiazolecarboxamide  2-[[((4-Hexyloxyphenyl) amino] carbonyl] amino] -4- methyl-N-(2,4,6- trimethylphenyl) -5- thiazolecarboxamide  2-[[((4-Hexyloxyphenyl) amino] carbonyl] amino] -4- methyl-N-(2,4,6- trimethylphenyl) -5- thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| (2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> 2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl] amino]-4-  [2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl] amino]-4-                                                                                                                                                                                                                                                                                                                                                                                              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2-[[((3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[((4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[((4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[((4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[((4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6- 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amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbonyl]amino]carbony                                                                                                                                                                                  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amino]carbonyl]amino]-4-                              | 256  256  257  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> 2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Fluoro-2-(trifluoromethyl)phenyl]]                                                                                                                                                                                                                                                                                                                                                                                                                                                     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<sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> | 256  H <sub>3</sub> C  H <sub>3</sub> C  CH <sub>3</sub> 2-[[[(3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide                                                                                                                                                                                                                       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amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Hexyloxyphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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| 5-thiazolecarboxamide  2-[[[(3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> 2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  4.15  Anino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[[4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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2-[[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[[4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trifluoromethyl)phenyl]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             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2-[[[(4-Fluoro-2-trimethylphenyl)-5-thiazolecarboxamide 
2-[[[(4-Fluoro-2-trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N- 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amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-                                                                                                                  | 256  2-[[[(3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl]]                                                                                                                                                                                                                                                                                                                                                                                                                                                                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2-[[(4-Fluoro-2-trimethylphenyl)] amino]carboxamide  2-[[(4-Fluoro-2-trimethylphenyl)] amino]carboxamide                                                                                                                                                                                                                                              
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 256  H <sub>3</sub> C  CH <sub>3</sub> 2-[[[(3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[[4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[[4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Hexyloxyphenyl) 4.42                                                                                                                                                                                                                                                                                                                                                                                                                      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amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Hexyloxyphenyl) 4.99  2-[[(4-Hexyloxyphenyl) 4.42  amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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2-[[((4-Hexyloxyphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| 2-[[[(3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> 2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl] amino]-4-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    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amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  257  CH <sub>3</sub> 2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[[4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 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amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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2-[[[(3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-methyl-N-(2,4,6-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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amino]carbonyl]amino]-4-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N 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amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-                                                                                                                    | 256 256 257 258 258 256 257 258 257 258 257 258 258 257 258 258 256 257 257 258 257 258 257 258 257 258 257 258 257 258 257 258 257 258 257 258 258 257 258 258 258 258 258 258 258 258 258 258                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 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2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 256  H <sub>3</sub> C  CH <sub>3</sub> 2-[[[(3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  257  CH <sub>3</sub> CH <sub>3</sub> 2-[[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  258  CH <sub>3</sub> CH <sub>3</sub> 2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  258  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> 2-[[[(4-Hexyloxyphenyl) 4.42                                                                                                                                                                                                                                                                                                                                                                     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2-[[[(4-Fluoro-2-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Hexyloxyphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Hexyloxyphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      
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| 2-[[[(3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> 2-[[((4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[((4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[([4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl] amino]-4-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 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amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 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<sub>3</sub>  
2-[[(4-Fluoro-2-trimethylphenyl)-5-thiazolecarboxamide   4.99     CH <sub>3</sub>   2-[[(4-Fluoro-2-trimethylphenyl)-4-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2,4,6-methyl-N-(2 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amino]carbonyl]amino]-4-                                                                                                                                                            | 256    CH <sub>3</sub>   2-[[[(3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide   4.12     CH <sub>3</sub>   2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide   4.15     CH <sub>3</sub>   2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide   4.15     CH <sub>3</sub>   2-[[(4-Fluoro-2-trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[[(4-Fluoro-2-(trifluoromethyl)phenyl]   4.99     CH <sub>3</sub>   2-[[(4-Fluoro-2-(trifluoromethyl)phenyl]   4.99     CH <sub>3</sub>   2-[[(4-Fluoro-2-(trifluoromethyl)phenyl]   4.99     CH <sub>3</sub>   2-[[(4-Fluoro-2-(trifluoromethyl)phenyl]   4.99     CH <sub>3</sub>   2-[[(4-Fluoro-2-(trifluoromethyl)phenyl]   4.99     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.99     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.99     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.99     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(1-Fluoro-2-(trifluoromethyl)phenyl]   4.15     CH <sub>3</sub>   2-[(                                                                                                                                                                                                                                                                                                                                                                                        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                             | 256    2-[[[(3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide   4.15                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[(4-Hexyloxyphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 256    CH <sub>3</sub>   2-[[[(3-Acetylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide   4.12     CH <sub>3</sub>   2-[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide   4.15     CH <sub>3</sub>   2-[[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide   4.99     CH <sub>3</sub>   2-[[[(4-Fluoro-2-trimethylphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide   4.42     CH <sub>3</sub>   2-[[((4-Hexyloxyphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide   4.42     CH <sub>3</sub>   2-[[((4-Hexyloxyphenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide   4.42     CH <sub>3</sub>   4.42   4.42     CH <sub>3</sub>   4.42   4.42     CH <sub>3</sub>   4.42   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42     CH <sub>3</sub>   4.42 |
| amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  4.15  Anino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[[4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                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trimethylphenyl)-5- thiazolecarboxamide  257  CH <sub>3</sub> CH <sub>3</sub> 2-[[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  4.15  And thiazolecarboxamide  2-[[(4-Fluoro-2- trimethylphenyl)-5- thiazolecarboxamide  2-[[(4-Fluoro-2- trimethylphenyl)-5- thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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thiazolecarboxamide  2-[[[(4-Hexyloxyphenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  4.15  And the second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second 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trimethylphenyl)-5- thiazolecarboxamide  257  CH <sub>3</sub> CH <sub>3</sub> 2-[[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  4.15  And thiazolecarboxamide  2-[[(4-Fluoro-2- trimethylphenyl)-5- thiazolecarboxamide  2-[[(4-Fluoro-2- trimethylphenyl)-5- thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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thiazolecarboxamide  2-[[[(4-Hexyloxyphenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| trimethylphenyl)-5- thiazolecarboxamide  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> 2-[[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   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methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5-  (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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<sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> 2-[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 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amino]carbonyl]amino]-4-methyl-N-(2,4,6-trifluoromethyl)phenyl]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          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2-[[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl)phenyl]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Hexyloxyphenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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| thiazolecarboxamide  CH <sub>3</sub> CH <sub>3</sub> 2-[[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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                                                       | 2-[[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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| 2-[[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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                                                       | 2-[[[(4-Cyanophenyl) amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide  2-[[[(4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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| 2-[[[(4-Cyanophenyl) amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[(4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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| amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide  2-[[[[4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 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                    | 258    CH3   trimethylphenyl)-5- thiazolecarboxamide    2-[[[4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide    2-[[(4-Hexyloxyphenyl) 4.42]   4.42   4.99                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  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| thiazolecarboxamide  H <sub>3</sub> C  2-[[[[4-Fluoro-2- (trifluoromethyl)phenyl] amino]carbonyl]amino]-4-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             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(trifluoromethyl)phenyl] amino]carbonyl]amino]-4- methyl-N-(2,4,6-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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2-[[[(4-Hexyloxyphenyl)amino]-4-methyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6-dethyl-N-(2,4,6- 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| H <sub>3</sub> c  2-[[[[4-Fluoro-2-(trifluoromethyl)phenyl]amino]-4-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   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methyl-N-(2,4,6- trimethylphenyl)-5-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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2-[[[(4-Hexyloxyphenyl) amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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260	0	4-[[[[4-Methyl-5-	4.26
260	o-K	[[(2,4,6-trimethyl-	4.20
1	H <sub>3</sub> C >	phenyl) amino]carbonyl]-	
	* 🖳	2-thiazolyl]-amino]-	
	)N CH <sub>2</sub>	carbonyl]amino]benzoic	
	od Jily "	acid ethyl ester	
	N S CH <sub>3</sub>		
ŀ	N J 113		
L	H₃ C CH₃		
261	H <sub>0</sub> C	2-[[[(4-Decylphenyl)-	
		amino]carbonyl]amino]-4-	
		methyl-N-(2,4,6-	
1		trimethylphenyl)-5- thiazolecarboxamide	
	. GH₃	CHIAZOTECATDOXAMITAE	
	S PO CH,		
	i de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de l		
	н, с С Сн,		
262	H₃C	4-Methyl-2-[[[(4-	4.71
		propylphenyl)amino]-	
	()	carbonyl]amino]-N- (2,4,6-trimethylphenyl)-	
	N	(2,4,6-trimethylphenyl)	
	o=\N_1CH <sub>3</sub>	- CHIAZOICCAIDONAMIAG	
	'N CLO		
	s T cH₃		
	H <sub>3</sub> C CH <sub>3</sub>		
263	CH.	4-Methyl-2-[[[(3,4,5-	4.67
203	Q 0-CH₃	trimethoxyphenyl)amino]-	
	H <sub>3</sub> C ,	carbonyl]amino]-N-	
		(2,4,6-trimethylphenyl)-	
	)N N CH3	5-thiazolecarboxamide	
	S CH <sub>3</sub>		
	N. J. 13		
	H <sub>3</sub> C CH <sub>3</sub>		
264	H <sub>3</sub> C	4-Methyl-2-[[[[4-[[(5-	4.27
	ON OF	methyl-3-isoxazolyl)	
	°	amino]sulfonyl]phenyl]-	
		amino]carbonyl]amino]-N-	
	N N-CH <sub>3</sub>	(2,4,6-trimethylphenyl)- 5-thiazolecarboxamide	
	N- S-O	 	
	" , K H3		
	. н₃с СН₃		

<u> </u>		IA FFFFA SC 13 3 7	T
265	\ ~4°	4-[[[[4-Methyl-5-	4.75
	<b>│</b>	[[(2,4,6-trimethyl	
	H <sub>3</sub> C-/	phenyl)amino]carbonyl]-	
	N A	2-thiazolyl]-	
ļ	of "MCH3	amino]carbonyl]-amino]-	
1	N N	benzoic acid butyl ester	
	l all all all all all all all all all a		
	"	·	
	H <sub>3</sub> C CH <sub>3</sub>		
266	H <sub>3</sub> C° V CH <sub>3</sub>	2-[[(1-Isoquinolinyl	0.01
200		amino)carbonyl]amino]-4-	3.81
		methyl-N-(2,4,6-	
	N. C.	trimethylphenyl)-5-	
	"N ~		
	o=( N→CH <sub>3</sub>	thiazolecarboxamide	1
	N-CAL CO		1
	S Y CH₃		
	l		
1	н₃с СН₃		
267	H <sub>3</sub> C	4-Methyl-2-[[[[2-	4.42
201		[(phenyl-methyl)thio]-	7.42
1	CH <sub>3</sub> CH <sub>3</sub> LLLL	phenyl]amino]carbonyl]-	ļ
	J S N N I	amino]-N-(2,4,6-	
	H <sub>2</sub> C-	trimethylphenyl)-5-	
	CH <sub>3</sub>	thiazolecarboxamide	<b>i</b> .
	G113		
	<b>*</b>	14 27 13 3 0 55554 515	
268		4-Methyl-2-[[[[4-[(5-	4.96
	<b>)</b>	phenoxypentyl)oxy]phenyl	
	ام	]amino]carbonyl]amino]-	
		N-(2,4,6-trimethyl-	
	-9_	phenyl)-5-thiazole-	
		carboxamide	
	L-Q		
	G, N, CH₃		
	'N-CLO		
	° Т сн <sub>з</sub>		
	<b>"</b>		
	н₃с Сн₃		
269	H <sub>5</sub> Ç	2-[[[[5-(1,1-Dimethyl-	5.76
209		propyl)-2-methoxy-	5.76
	H <sub>3</sub> Ç CH <sub>3CH<sub>3</sub></sub>	phenyl]amino]carbonyl]-	
	N N H <sub>3</sub> C	amino]-4-methyl-N-	
	CH3 Y S NO	(2,4,6-trimethylphenyl)-	
	N N	5-thiazolecarboxamide	
1	H <sub>3</sub> C	2 CITESOTECAT DOVAMENCE	
1	CH <sub>3</sub>		

270	H <sub>3</sub> C OCH <sub>3</sub>	2-[[(1,2-Dihydro-5- acenaphthylenyl)amino]ca rbonyl]amino]-4-methyl- N-(2,4,6-trimethyl- phenyl)-5-thiazole- carboxamide	4.70
271	H <sub>3</sub> C  N  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> H <sub>3</sub> C  CH <sub>3</sub>	4-Methyl-2-[[[(3-phenoxyphenyl)amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.70
272	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	4-Methyl-2-[[[[2-(4-morpholinyl)phenyl]-amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.01
273	N CH <sub>3</sub> O CH <sub>3</sub> N CH <sub>3</sub> CH <sub>3</sub>	4-Methyl-2-[[[[2-(1-piperidinyl)phenyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	5.55
274	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> H <sub>3</sub> C	2-[[[(1-Acetyl-2,3-dihydro-1H-indol-6-yl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	4.08

		10 11110 = -	1
275	H <sub>3</sub> C Br	2-[[[(2-Bromo-5-methoxyphenyl)amino]car-	4.55
		bonyl]amino]-4-methyl-N-	
	N N CH₃	(2,4,6-trimethylphenyl)-	
		5-thiazolecarboxamide	
	s s	Chiazoicearboxamiae	
	°		
1			
	н₃с Сн₃		
276	0	2-[[[(2,3-Dimethyl-1H-	4.30
	l l l l l l l l l l l l l l l l l l l	indol-5-yl)amino]	
	N CH3	carbonyl]amino]-4-	
1	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	methyl-N-(2,4,6-	
1		trimethyl phenyl)-5-	
	)=( <sub>au</sub> ·	thiazolecarboxamide	ŀ
	H₃Ç N-√ CH₃		
	<b>&gt;=</b> ⟨ _0		
	<b>⟨ / CH</b> <sub>3</sub>		
	H <sub>3</sub> C	14 26 11 1 0 11110 1111	1.00
277		4-Methyl-2-[[[[2-[[(1-	4.82
		methylethyl)amino]carbo-	<b> </b> .
	l h l	nyl]phenyl]amino]car-	
1.		bonyl]amino]-N-(2,4,6-	
	S H C CH3	trimethylphenyl)-5-	
	/ `~ '180 °	thiazolecarboxamide	
	H <sub>3</sub> C N-C CH <sub>3</sub>		
-			
	Lina Cha		
	н, с		
278		2-[[[(3-Bromo-2-methyl-	4.60
12.0	l R [ ]	phenyl)amino]carbonyl]-	1.00
İ	Br Br	amino]-4-methyl-N-	
I	CH <sub>3</sub>	(2,4,6-trimethylphenyl)-	
	s~N 2113	5-thiazolecarboxamide	
1			
1	H₃C N-√ CH₃		
1	(°)		
1	<b>⟨ ⟩</b> —cн₃		
	) <u>-</u> "		
	H₃C		
279	CH <sub>3</sub> H <sub>3</sub> C	2-[[[(4-Methoxybutyl)	7.62
	HC Q LL LANG	amino]carbonyl]amino]-4-	
	"" " " " CH3	methyl-N-(2,4,6-	
	ngo	trimethylphenyl)-5-	
		thiazolecarboxamide	
280	CH <sub>3</sub> H <sub>3</sub> Ç	2-[[[(3,3-Dimethyl-	9.13
	H <sub>2</sub> C <sub>2</sub> H <sub>3</sub>	butyl)amino]carbonyl]-	
	H3C NN STIT ACH.	amino]-4-methyl-N-	
]	H <sub>C</sub>	(2,4,6-trimethylphenyl)-	
		5-thiazolecarboxamide	

281	H <sub>3</sub> C CH <sub>3</sub> N CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	4-Methyl-2-[[[(2-methylbutyl)amino]-carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.90
282	H <sub>3</sub> CCH <sub>3</sub> H <sub>3</sub> CCH <sub>3</sub> H <sub>3</sub> CCH <sub>3</sub> CH <sub>3</sub>	4-Methyl-2-[[[(3-methylbutyl)amino]carbo-nyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide	8.98
283	H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub>	2-[[(2-Methoxyethyl)- amino]carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	7.30
284	H <sub>3</sub> C N N N S N H <sub>3</sub> C CH <sub>3</sub>	2-[[[2-(Dimethyl- amino)ethyl]amino]- carbonyl]amino]-4- methyl-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	5.73
285	H <sub>3</sub> C S N N S N S N H <sub>3</sub> C CH <sub>3</sub>	4-Methyl-2-[[[[2- (methylthio)ethyl]amino] carbonyl]amino]-N- (2,4,6-trimethylphenyl)- 5-thiazolecarboxamide	8.19

### Examples 286 to 311

#### General Procedure

5

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Compounds 286 to 311 with the exception of compound 307 were prepared following the procedure described below.

A solution of 2-[[(Butylamino)carbonyl]amino]-4-methyl-5-thiazole carboxylic acid chloride (30 mg, 0.11 mmol), appropriate amine (0.12 mmol) in THF (1 mL) was treated with diisopropylethyl amine (22.6  $\mu$ L, 0.13 mmol). The mixture was purged with argon and stirred mechanically in a vial for 22 h, diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (3x). The organic extract was separated, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The crude products were purified either by truturation with dichloromethane-ether (1:1) or by silica gel

chromatography (elution solvent: 80% EtOAc in hexanes followed by EtOAc) or by automatic preparative HPLC (conditions: YMC S5 ODS A 20 x 100 mm Column, 10 min gradient starting from 30% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.1% TFA) and 70% solvent A (10% MeOH, 90% H<sub>2</sub>O, 5 0.1% TFA) to 100% solvent B, flow rate 20 mL/min,  $\lambda = 220$  nM. Compound 307 was prepared following the procedure described below. A suspension solution of 2-[[(Butylamino)carbonyl]amino]-4-methyl-5thiazole carboxylic acid (100 mg, 0.36 mmol), and HATU (170 mg, 0.44 mmol) in DMF (3 mL) was treated with diisopropylethyl amine (62 mL, 0.44 mmol). The mixture was heated to 60°C for 2 h, cooled, diluted with 10 dichloromethane (12 mL), washed with 8M aq. Urea solution in 2 N aq. HCl (6 mL, 3x), 5% aq. KHCO, solution (6 mL, 3x), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was triturated with EtOAc-ether to obtain the mixed anhydride intermediate (102 mg, 74%) as a white solid. A 1 M solution of sodium bis(trimethylsilylamide) in THF (170  $\mu$ L, 0.17 mmol) 15 was added dropwise to a stirred solution of 2,6-dichloroaniline (19.4 mg, 0.12 mmol) in THF (1 mL). After 15 min, the mixed anhydride intermediate (41.3 mg, 0.11 mmol) was added in one portion. A few drops of DMF was added and the solution was stirred for 16 h. Additional 1 M solution of sodium bis(trimethylsilylamide) (110 µL) was added and the 20 mixture was stirred for additional 2 h. The mixture was diluted with dichloromethane (4 mL) and washed with 2 N aq. HCl solution (2 mL, 3x), satd. aq. KHCO, solution (3x), dried (Na, SO,), filtered and concentrated. The solid was washed with hexanes (2x) and the residue was chromatographed on a silica gel column. Elution with 80% EtOAc in 25 hexanes followed by EtOAc afforded 307 (12 mg, 27%) as a light tan solid. "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H,O, 0.2% H,PO,) to 100% solvent B (90% MeOH, 10%  $H_2O$ , 0.2%  $H_3PO_4$ ), flow rate 4 mL/min,  $\lambda = 220$ 30 nM.

P= > c	10.	10	LUDIC
EX.	Compound Structure	Compound Name	HPLC
NO.			Ret Time
000	-~~	2-[[(Butylamino)	(min)
286	н,с , о , , , , , , , , , , , , , , , , ,	carbonyl]amino]-N-(2,3-	4.20
	Thu	dihydro-1H-inden-5-yl)-	1
		4-methyl-5-thiazole-	
-	N N	carboxamide	
287		2-[[(Butylamino)	4.20
	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	carbonyl]amino]-N-2-	
	0. [ > N	naphthalenyl-4-methyl-	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	5-thiazolecarboxamide	
288	O /-CH <sub>3</sub>	2-[[(Butylamino)	4.24
	H <sub>3</sub> C N N	carbonyl]amino]-N-(3-	
	0 1 N "	hydroxy-2-naphtha-	
	он Т	lenyl)-4-methyl-5-	
	N N	thiazolecarboxamide	
289	₩c	2-[[(Butylamino)	3.95
203	H <sub>3</sub> C Q N	carbonyl]amino]-N-(2-	5.55
		fluoro-5-methylphenyl)-	
	CH <sub>3</sub>	4-methyl-5-	
	F	thiazolecarboxamide	
200	C CH <sub>3</sub>	2-[[(Butylamino)	2.70
290	H3C_N & ~ C113	carbonyl]amino]-N-(2,6-	3.78
		dimethylphenyl)-4-	
	CH-S' "	methyl-5-thiazole-	
	Ň	carboxamide	
	<b>℃</b> `CH <sub>3</sub>		
291		N-(4-Bromo-2-	4.12
		methylphenyl)-2- [[(butylamino)carbonyl]	
	ا	amino]-4-methyl-5-	
	" \N-(~) ~0	thiazolecarboxamide	
	CH <sub>3</sub>		
	H <sub>3</sub> C—/		

292	H <sub>3</sub> C  N  N  CH <sub>3</sub> Br  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N-(3-Bromo-2,4,6- trimethylphenyl)-2- [[(butylamino)carbonyl] amino]-4-methyl-5- thiazolecarboxamide	4.28
293		2-[[(Butylamino) carbonyl]amino]-N-[2,6- dimethyl-3-(1- methylethyl)phenyl]-4- methyl-5- thiazolecarboxamide	4.28
294	H³C CH³ N N N CH³	N-(2-Bromo-4,6- dimethylphenyl)-2- [[(butylamino)carbonyl] amino]-4-methyl-5- thiazolecarboxamide	4.00
295	H <sub>3</sub> C	3-[[[2-[[(Butylamino) carbonyl]amino]-4- methyl-5-thiazolyl]- carbonyl] amino]-4- methyl-2-thiophene- carboxylic acid methyl ester	3.83
296	H <sub>3</sub> C N N N N CH <sub>3</sub>	2-[[(Butylamino) carbonyl]amino]-4- methyl-N-(2-methyl-6- quinolinyl)-5- thiazolecarboxamide	2.98
297	H <sub>3</sub> C <sub>1</sub> O <sub>N</sub> NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	2-[[(Butylamino) carbonyl]amino]-N-(2,6- dimethoxyphenyl)-4- methyl-5-thiazolecar- boxamide	3.39
298	H <sub>3</sub> C <sub>1</sub> N <sub>1</sub> O <sub>1</sub> CH <sub>3</sub>	2-[[(Butylamino) carbonyl]amino]-N-(4- methoxy-2-naphtha- lenyl)-4-methyl-5- thiazolecarboxamide	4.31

	T	T	
299	H <sub>3</sub> C N O CH <sub>3</sub> C CH <sub>3</sub>	2-[[(Butylamino) carbonyl]amino]-N-(2- methyl-1-naphthalenyl)- 4-methyl-5-thiazole- carboxamide	3.92
300	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	2-[[(Butylamino) carbonyl]amino]-N-[4- (dimethylamino)- 2,3,5,6-tetramethyl- phenyl]-4-methyl-5- thiazolecarboxamide	3.14
301	CH <sub>3</sub> O	2-[[(Butylamino) carbonyl]amino]-N-(6- methyl-5-quinolinyl)-4- methyl-5- thiazolecarboxamide	3.13
302	OH OHS N N N CH3	2-[[(Butylamino) carbonyl]amino]-N-[2- (2-hydroxyethyl)-6- methylphenyl]-4-methyl- 5-thiazolecarboxamide	3.50
303	H <sub>3</sub> C	2-[[(Butylamino) carbonyl]amino]-N-(2,6- dimethyl-3- nitrophenyl)-4-methyl- 5-thiazolecarboxamide	3.75
304	H <sub>3</sub> C N S N S	N-(2-Bromo-3,4,6- trimethylphenyl)-2- [[(butylamino)carbonyl] amino]-4-methyl-5- thiazolecarboxamide	4.12
305	H <sub>3</sub> C N N N N N N N N N N N N N N N N N N N	N-(2-Acetyl-6- hydroxyphenyl)-2- [[(butylamino)carbonyl] amino]-4-methyl-5- thiazolecarboxamide	3.75

306	H₃C√CH₃	[4-[[[2-[[(Butylamino)	4.10
	H <sub>3</sub> C CH <sub>3</sub> N  H <sub>3</sub> C CH <sub>3</sub> N  CH <sub>3</sub> CH <sub>3</sub> N	carbonyl]amino]-4- methyl-5-thiazolyl]- carbonyl] amino]- 2,3,5,6-tetramethyl- phenyl]carbamic acid 1,1-dimethylethyl ester	
307	H <sub>3</sub> C N N S OCH 3	2-[[(Butylamino) carbonyl]amino]-N-(2,6- dichlorophenyl)-4- methyl-5- thiazolecarboxamide	4.42
308	H <sub>3</sub> C NH <sub>2</sub> CH <sub>3</sub> H <sub>3</sub> C CH <sub>3</sub> NH <sub>2</sub>	N-(4-Amino-2,3,5,6- tetramethylphenyl)-2- [[(butylamino)carbonyl] amino]-4-methyl-5- thiazolecarboxamide	3.15
309	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub>	<pre>dimethylphenyl]-2- [[(butylamino)carbonyl]</pre>	3.52
310	H <sub>3</sub> C CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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311	H <sub>3</sub> C	2-[[(Butylamino) carbonyl]amino]-N-(2- chloro-6-methylphenyl)- 4-methyl-5- thiazolecarboxamide	4.51

Example 312

### Preparation of 4-Methyl-2-[(methylsulfonyl)amino]-N-(2,4,6-

### trimethylphenyl)-5-thiazolecarboxamide

A. Ethyl-2-[(methylsulfonyl)amino]-4-methyl-thiazole-5-carboxylate
A stirred solution of ethyl-2-amino-4-methyl-thiazole-5-carboxylate (558 mg, 3 mmol) in dichloromethane (15 mL) and pyridine (5 mL) was treated with methanesulfonyl chloride (687 mg, 6 mmol) at rt overnight. The solution was diluted with dichloromethane (50 mL) and washed with 2N aq. HCl solution (15 mL, 3x), dried (MgSO<sub>4</sub>), filtered and concentrated. The crude residue was diluted with ether (25 mL) and the solid was filtered, washed with 1:1 ether:hexane mixture (10 mL, 3x), and dried in vacuo to obtain the title compound (687 mg, 87%) as an off-white solid.

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B. 2-[(Methylsulfonyl)amino]-4-methyl-thiazole-5-carboxylic acid
A stirred solution of Ethyl-2-[(methylsulfonyl)amino]-4-methyl-thiazole-5-carboxylate (300 mg, 1.14 mmol) in methanol (9 mL) was treated with a 1N NaOH solution (28.4 mL, 28.4 mmol). The mixture was stirred at rt overnight. The solution was cooled to 0 °C and acidified with 6N aq. HCl solution to pH 1. The solution was extracted with dichloromethane-chloroform mixture. The organic extract was dried (MgSO4), filtered and concentrated in vacuo to obtain the title acid (148 mg, 55%).

# 20 <u>C.4-Methyl-2-[(methylsulfonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide</u>

Diisopropylethylamine (87 μL, 0.5 mmol) was added to a solution of **312 B** (99 mg, 0.42 mmol), 2,4,6-trimethylaniline (68 μL, 0.5 mmol), and [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate (HATU, 191 mg, 0.5 mmol) in DMF (3 mL). The mixture was stirred at rt overnight, diluted with EtOAc and washed with 0.5 N aq. HCl solution (15 mL), 10% aq. LiCl solution (25 mL, 3x), water (930 mL, 2x), brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was chromatographed on a silica gel column and eluted with 50% EtOAc in hexanes, followed by

75% EtOAc in hexanes and 2% MeOH in EtOAc to obtain the title compound (19 mg, 13%) as a white solid.

### Example 313

5 Preparation of 4-Methyl-2-[[(phenylamino)thiocarbonyllamino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

A solution of 2 (45 mg, 0.16 mmol) and phenylisothiocyanate (43 mg, 0.32 mmol) in pyridine (2 mL) was heated to 80°C for 20 h. The mixture was cooled, diluted with dichloromethane-THF mixture (80 mL, 3:1) and washed with 2 N aq. HCl solution (15 mL, 2x). The organic extract was dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was diluted with EtOAc (20 mL) and the solid was filtered, washed with ether (10 mL, 3x), and dried *in vacuo* to obtain the title compound (35 mg, 52%) as an offwhite solid.

### Example 314

Preparation of 2-[[(Ethylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

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Compound 314 was prepared by an analogous method as that of compounds 171-180, using ethylisocyanate to give the title compound 314 as a white solid (65%).

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### Example 315

### <u>Preparation of N-(2-Chloro-6-methylphenyl)-2-</u> [(cyclopropylcarbonyl)amino]-5-thiazolecarboxamide

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A. Ethyl-2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate A suspension of ethyl-2-amino-thiazole-5-carboxylate (972 mg, 6 mmol, B. Plouvler, C. Bailly, R. Houssin, j-P. Henlchart Heterocyles 32(4), 693-701, 1991 and H. J. Becker, J. de Jonge Rec. Trav. Chim, 61, 463, 1942), di-t-butyldicarbonate (1.94 g, 9 mmol) and 4-dimethylaminopyridine (73 mg, 0.6 mmol) in dry tetrahydrofuran (75 mL) was stirred under nitrogen for 24 h. The solvent was evaporated in vacuo. The residue was suspended in ether (50 mL). The solid was washed with ether (10 mL, 3x), and dried in vacuo to obtain the title compound (1.1 g, 70%).

### B. 2-tert-butoxycarbonyloxyamino-thiazole-5-carboxylic acid

A stirred solution of ethyl-2-tert-butoxycarbonyloxyamino-4-methyl-thiazole-5-carboxylate (1.1 g, 4.2 mmol) in tetrahydrofuran-methanol (80 mL, 1:1) was treated with a 6N aq. NaOH solution (20 mL, 120 mmol). The mixture was stirred at rt for 24 h. Most of THF and methanol were removed by distillation under reduced pressure and the aq. Solution was acidified with 6 N aq. HCl solution (22 mL). The precipitated solid was filtered, washed with water and ether, air dried followed by drying in vacuo to obtain the title acid (940 mg, 96%) as an off-white solid.

C. [5-[[(2-chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester

A 2 M solution of oxalyl chloride in dichloromethane (1 mL, 2 mmol) was added dropwise to a stirred solution of 2-tert-butoxycarbonyloxyamino-

- thiazole-5-carboxylic acid (234 mg, 1 mmol) in THF (10 mL) and N,N-dimethyl formamide (few drops). The solution was stirred at rt for 4 h. The solvent was evaporated under reduced pressure, and *in vacuo* to obtain the crude acid chloride.
- 2-Chloro-6-methyl aniline (212 mg, 1.5 mmol) was added dropwise to a

  stirred solution of crude 2-tert-butoxycarbonyloxyamino-thiazole-5carboxylic acid chloride (1 mmol) in dichloromethane (10 mL) at 0°C.

  Diisopropylethylamine (516 mg, 4 mmol) was added. The solution was allowed to warm to rt and stirred for 24 h, diluted with dichloromethane (60 mL) and washed with 2 N aq. HCl solution (15 mL). The organic extract was dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was diluted with EtOAc-ether (25 mL, 1:4) and the solid was filtered and washed with ether (5 mL, 4x), and dried in vacuo to obtain the title compound (175 mg, 48%) as a tan solid.
- 20 D. 2-Amino-N-(2-chloro-6-methylphenyl)- 5-thiazolecarboxamide Compound 315D was prepared by an analogous method as that of 2, except using compound 315C to give the title compound 315D as a tan solid.
- 25 <u>E. 2-[(Cyclopropylcarbonyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide</u>

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A solution of **315D** (50.6 mg, 0.19 mmol) and cyclopropanecarboxylic acid anhydride (302 mg, 1.96 mmol) in dioxane (2 mL) was heated to 93 °C overnight. The mixture was concentrated *in vacuo*, diluted with EtOAc and washed with satd. aq. KHCO<sub>3</sub> solution (2x). The organic extract was

dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was triturated with ether to obtain the title compound (11 mg, 17%) as a white solid.

#### Example 316

5 <u>Preparation of 2-[[[(1,1-Dimethylethyl)amino]carbonyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide</u>

Sodium hydride (19.2 mg, 0.8 mmol) was added to a solution of 315D (48.3 mg, 0.18 mmol) and t-butylisocyanate (41  $\mu$ L, 0.36 mmol) in THF (5 mL) at 0 °C. After 1 h, the mixture was diluted with EtOAc and washed with cold satd. aq. ammonium chloride solution. The aqueous layer was separated and extracted with EtOAc. The EtOAc extracts were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was purified by automatic preparative HPLC (conditions: YMC S5 ODS A 20 x 100 mm Column, 10 min gradient starting from 10% solvent B (90% MeOH, 10% H2O, 0.1% TFA) and 90% solvent A (10% MeOH, 90% H2O, 0.1% TFA) to 100% solvent B, flow rate 20 mL/min,  $\lambda$  = 220 nM to obtain the title compound (18 mg, 28%) as an off-white solid.

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### Example 317

<u>Preparation of 2-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazoleacetamide</u>

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Compound 317 was prepared by an analogous method as that of 1, except using methyl-2-amino-4-methyl-thiazole-5-acetate to give the title compound 317 as an off-white solid.

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### Example 318

## $\underline{\textbf{Preparation of 2-Amino-4-methyl-N-(2,4,6-trimethylphenyl)-5-}}$

thiazoleacetamide

10 Compound 318 was prepared by an analogous method as that of 2, except using 317 to give the title compound 318 as a light brown solid.

### Example 319

# <u>Preparation of N-(2-Chloro-6-methylphenyl)-2-[(4,6-dimethyl-2-pyridinyl)amino]-5-thiazolecarboxamide</u>

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### A. 2-Bromo-N-(2-chloro-6-methylphenyl)- 5-thiazolecarboxamide

A solution of copper (II) bromide (2.68 g, 12 mmol) in acetonitrile (50 mL) was purged with nitrogen and cooled to 0 °C. t-Butyl nitrite (2 mL, 15 mmol) was added, followed by a solution of compound 315D (2.68 g, 10 mmol) in acetonitrile (50 mL), The mixture was stirred at rt overnight and concentrated in vacuo. The residue was dissolved in EtOAc, washed with satd. aq. NaHCO<sub>3</sub> solution and the precipitate was removed by filtration. The organic extract was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was crystallized from EtOAc/ether/hexanes mixture to obtain the title compound (1.68 g, 51%) as a yellow solid.

# B. N-(2-Chloro-6-methylphenyl)-2-[(4,6-dimethyl-2-pyridinyl)amino]-5-thiazolecarboxamide

95% Sodium hydride (15 mg) was added to a mixture of 319A (25 mg, 0.075 mmol) and 4,6-dimethyl-2-aminopyridine (37 mg, 0.302 mmol) in THF (1 mL). The mixture was heated to 60  $^{\circ}$ C overnight, cooled to rt and diluted with satd. aq. ammonium chloride solution. The mixture was extracted with EtOAc (2x). Organic extracts were combined, washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was triturated with ether to obtain the title compound (17.5 mg, 63%) as a tan solid.

### Example 320

# <u>Preparation of N-(2-Chloro-6-methylphenyl)-2-[(4-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide</u>

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Compound 320 was prepared by an analogous method as that of 319B, except using 4-ethyl-2-aminopyridine to give the title compound 320.

### Example 321

# Preparation of N-(2-Chloro-6-methylphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide

Compound 321 was prepared by an analogous method as that of 319B,

except using 2,6-dimethyl-4-aminopyrimidine to give the title compound

321.

### Example 322

# $\frac{Preparation\ of\ N-(2-Chloro-6-methylphenyl)-2-(3-pyridazinylamino)-5-}{thiazolecarboxamide}$

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Compound 322 was prepared by an analogous method as that of 319B, except using 3-aminopyridazine to give the title compound 322.

#### **Examples 323 to 335**

10 General Procedure

Compounds 323 to 335 were prepared following the procedure described below. Diisopropylethyl amine (60  $\mu$ L, 0.34 mmol) was added to a mixture of amine 144 (31 mg, 0.11 mmol), appropriate carboxylic acid (0.13 mmol), 1-hydroxy-7-azabenzotriazole (19.5 mg, 0.14 mmol), and ethyl-3-(3-

dimethylamino)-propyl carbodiimide hydrochloride (26.8 mg, 0.14 mmol) in THF (0.4 mL). The mixture was heated in a sealed tube under argon at 50 °C for 24 h. The reaction mixture was diluted with dichloromethane (4 mL) and washed with 1 N aq. HCl solution. The dichloromethane solution was passed through a Varian Mega Bond Elut SCX cation exchange

column (prewashed with methanol and equilibrated with acctonity location).

column (prewashed with methanol and equilibrated with acetonitrile-methanol (4:1). The column was eluted sequentially with acetonitrile-methanol (4:1), methanol-2M methanolic ammonia (4:1). Fractions containing the product were combined and concentrated in vacuo. "HPLC Ret Time" is the HPLC retention time under the following

conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H2O, 0.2% H3PO4) to

100% solvent B (90% MeOH, 10% H2O, 0.2% H3PO4), flow rate 4 mL/min,  $\lambda$  = 220 nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
323	S P <sub>3</sub> C	N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2-thienyl-carbonyl)amino]-5-thiazolecarboxamide	3.70
324	N S P CH3 CH	N-(2-Chloro-6-methylphenyl)-2- [(cyclopropylcarbonyl)amino]-4- methyl-5-thiazolecarboxamide	3.41
325	CH <sub>3</sub> Cl N S N N	N-(2-Chloro-6-methylphenyl)-4- methyl-2-[(2-furanyl- carbonyl)amino]-5- thiazolecarboxamide	3.49
326	S P <sub>3</sub> C	N-(2-Chloro-6-methylphenyl)-4- methyl-2-[(3-thienylcar- bonyl)amino]-5-thiazole- carboxamide	3.71
327	CH <sub>3</sub> Cl	N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(3-furanylcarbonyl)amino]-5-thiazolecarboxamide	3.57
328	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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329	Me CH <sub>3</sub> Cl	N-(2-Chloro-6-methylphenyl)-4-methyl-2-[[(2-methylcyclo-propyl)carbonyl]amino]-5-thiazolecarboxamide	3.65
330	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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331	O N S N CI	N N-(2-Chloro-6-methylphenyl)- 2-[(cyclopentylcarbonyl)amino]-4- methyl-5-thiazolecarboxamide	3.82
332	N S P <sub>3</sub> CI	N-(2-Chloro-6-methylphenyl)-4- methyl-2-[(2-methyl-1- oxopropyl)amino]-5- thiazolecarboxamide	3.50
333	N S H <sub>3</sub> C	N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(1-oxopentyl)amino]-5-thiazolecarboxamide	3.79
334	N S P3 CI	N-(2-Chloro-6-methylphenyl)-4- methyl-2-[(2-methyl-1- oxopentyl)amino]-5- thiazolecarboxamide	3.90
335	N S A3 CI	2-(Benzoylamino)-N-(2-chloro-6-methylphenyl)-4-methyl-5-thiazolecarboxamide	3.79

Examples 336 to 362

### General Procedure

- Compounds 336 to 362 were prepared by an analogous method as that of 323-335, except using 315D in place of 144. The crude products were purified by automatic preparative HPLC (conditions: YMC S5 ODS A 20 x 100 mm Column, 10 min gradient starting from 10% solvent B (90% MeOH, 10% H2O, 0.1% TFA) and 90% solvent A (10% MeOH, 90% H2O,
- 10-0.1% TFA ) to 100% solvent B, flow rate 20 mL/min,  $\lambda=220$  nM to obtain the title compounds 336-362.
  - "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS  $4.6 \times 50$  mm Ballastic Column, 4 min gradient starting from 100% solvent A (10% MeOH, 90% H2O, 0.2% H3PO4) to
- 15 100% solvent B (90% MeOH, 10% H2O, 0.2% H3PO4), flow rate 4 mL/min,  $\lambda = 220 \text{ nM}$ .

EX.	Compound Structure	Compound Name	HPLC
NO.	Compound Structure	Compound Name	Ret Time
10.			(min)
336	I N S N S	N-(2-Chloro-6-methylphenyl)-2- [(1-oxopropyl)amino]-5- thiazolecarboxamide	3.53
337	P P P P P P P P P P P P P P P P P P P	N-(2-Chloro-6-methylphenyl)-2- [(1-oxobutyl)amino]-5- thiazolecarboxamide	3.61
338	N S Rac	N-(2-Chloro-6-methylphenyl)-2- [(2-ethyl-1-oxobutyl)amino]-5- thiazolecarboxamide	3.54
339	Ph A <sub>3</sub> c	N-(2-Chloro-6-methylphenyl)-2- [[(1-phenylcyclo- propyl)carbonyl]amino]-5- thiazolecarboxamide	3.86
340	Me A <sub>3</sub> c	N-(2-Chloro-6-methylphenyl)-2- [[(1-methylcyclo- propyl)carbonyl]amino]-5- thiazolecarboxamide	3.53
341	CI NE P3 C	N-(2-Chloro-6-methylphenyl)-2- [[(2,2-dichloro-1-methylcyclo- propyl)carbonyl]amino]-5- thiazolecarboxamide	3.53
342	Me P <sub>3</sub> C	N-(2-Chloro-6-methylphenyl)-2- [[(2-methylcyclo- propyl)carbonyl]amino]-5- thiazolecarboxamide	3.53
343	OH H3c	N-(2-Chloro-6-methylphenyl)-2- [[(1-hydroxycyclopropyl)- carbonyl]amino]-5-thiazole- carboxamide	3.58
344	Me Me Me R <sub>3</sub> c	N-(2-Chloro-6-methylphenyl)-2- [[(2,2,3,3-tetramethylcyclo- propyl)carbonyl]amino]-5- thiazolecarboxamide	3.69

345	CN P <sub>3</sub> C	N-(2-Chloro-6-methylphenyl)-2- [[(1-cyanocyclopropyl)- carbonyl]amino]-5-thiazole- carboxamide	3.53
346	I N S N S N S N S N S N S N S N S N S N	N-(2-Chloro-6-methylphenyl)-2- [(cyclobutylcarbonyl)amino]-5- thiazolecarboxamide	3.52
347	I N S N CI	N-(2-Chloro-6-methylphenyl)-2- [(cyclopentylcarbonyl)amino]-5- thiazolecarboxamide	3.59
348	A <sub>s</sub> c C	N-(2-Chloro-6-methylphenyl)-2- [(cyclohexylcarbonyl)amino]-5- thiazolecarboxamide	3.78
349	C I N S N S	N-(2-Chloro-6-methylphenyl)-2- [(phenylacetyl)amino]-5- thiazolecarboxamide	3.62
350		N-(2-Chloro-6-methylphenyl)-2- [(cyclohexylacetyl)amino]-5- thiazolecarboxamide	4.07
351		N-(2-Chloro-6-methylphenyl)-2- [(4-pyridinylacetyl)amino]-5- thiazolecarboxamide	3.75
352	Me H Me	N-(2-Chloro-6-methylphenyl)-2- [[(2,5-dimethyl-1H-pyrrol-3- yl)carbonyl]amino]-5- thiazolecarboxamide	3.17
353	N S N N	N-(2-Chloro-6-methylphenyl)-2- [(2-pyridinylcarbonyl)amino]-5- thiazolecarboxamide	3.07
354	N S N	N-(2-Chloro-6-methylphenyl)-2- [(3-pyridinylcarbonyl)amino]-5- thiazolecarboxamide	3.07

355		N-(2-Chloro-6-methylphenyl)-2- [(4-pyridinylcarbonyl)amino]-5- thiazolecarboxamide	3.61
356	ST NS PACE	N-(2-Chloro-6-methylphenyl)-2- [(3-thienylcarbonyl)amino]-5- thiazolecarboxamide	3.60
357	S Pac	N-(2-Chloro-6-methylphenyl)-2- [(2-thienylcarbonyl)amino]-5- thiazolecarboxamide	3.61
358	NS Asc	N-(2-Chloro-6-methylphenyl)-2- [(2-furanylcarbonyl)amino]-5- thiazolecarboxamide	3.61
359		N-(2-Chloro-6-methylphenyl)-2- [(3-furanylcarbonyl)amino]-5- thiazolecarboxamide	3.69
360		trans-N-(2-Chloro-6- methylphenyl)-2-[[(2- phenylcyclopropyl)carbonyl]amin o]-5-thiazolecarboxamide	3.98
361		N-(2-Chloro-6-methylphenyl)-2- [(2-methyl-1-oxopentyl)amino]-5- thiazolecarboxamide	3.90
362	Pac Pac	2-(Benzoylamino)-N-(2-chloro-6- methylphenyl)-5- thiazolecarboxamide	3.61

### Example 363

## $\underline{Preparation\ of\ 2\text{-}[(Cyclopropylcarbonyl)amino]\text{-}N\text{-}(2,6\text{-}dimethylphenyl)\text{-}5\text{-}}$

### $\underline{thiazole carboxamide}$

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Compound 363 was prepared by an analogous method as that of 315, except using 2,6-dimethylaniline to give the title compound 363.

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### Example 364

# <u>Preparation of 2-[(Cyclopropylcarbonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide</u>

10 Compound 364 was prepared by an analogous method as that of 315, except using 2,4, 6-trimethylaniline to give the title compound 364.

### Example 365

Preparation of N-(2-Chloro-4,6-dimethylphenyl)-2-

[(cyclopropylcarbonyl)amino]-5-thiazolecarboxamide

Compound **365** was prepared by an analogous method as that of **315**, except using 2-chloro-4,6-dimethylaniline to give the title compound **365**.

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#### Example 366

<u>Preparation of [4-[2-Oxo-2-[(2,4,6-trimethylphenyl)amino]ethyl]-2-</u> <u>thiazolyl]carbamic acid 1,1-dimethylethyl ester</u>

Compound 366 was prepared by an analogous method as that of 1 except, using 2-tert-butoxycarbonyloxyamino-thiazole-4-acetic acid to give the title compound 366 as a white solid.

### Example 367

Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-4-thiazoleacetamide

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Compound 367 was prepared by an analogous method as that of 4, except using 365 to give the title compound 367 as a white solid.

### Example 368

Preparation of 2-Methyl-5-nitro-N-(2,4,6-trimethylphenyl)benzamide

Compound 368 was prepared by an analogous method as that of 3, except using 2-methyl-5-nitrobenzoic acid to give the title compound 368 as a white solid.

#### Example 369

Preparation of 5-Amino-2-methyl-N-(2,4,6-trimethylphenyl)benzamide

5 10% Palladium on charcoal (30 mg) was added to a stirred solution of 368 (149 mg, 0.5 mmol) in EtOAc (50 mL). The reaction flask was equipped with a hydrogen filled balloon via a three-way stopcock. Air inside the flask was evacuated under reduced pressure and the flask filled with hydrogen from the balloon. After 4 h, the catalyst was filtered, washed with EtOAc (5 mL, 5x). The filtrate was concentrated to obtain the title compound (133 mg, 99%) as a white solid.

### Example 370

Preparation of 2-Amino-5-chloro-N-(2,4,6-trimethylphenyl)- 4-

15 <u>pyrimidinecarboxamide</u>

20

Compound 370 was prepared by an analogous method as that of 3, except using 2-amino-5-chloro-pyrimidine-4-carboxylic acid to give the title compound 370 as a white solid.

#### Example 371

Preparation of [4-Methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]- 2oxazolyl]carbamic acid 1,1-dimethylethyl ester

Compound 371 was prepared by an analogous method as that of 1, except using 2-*tert*-butoxycarbonyloxyamino-4-methyl-5-oxazolecarboxylic acid to give the title compound 371 as a light yellow foam.

#### Example 372

## Preparation of 2-Amino-4-(methyl)-N-(2,4,6-trimethylphenyl)-5-

#### oxazolecarboxamide, trifluoroacetate (1:1)

10

5

Compound 372 was prepared by an analogous method as that of 4, except using 369 to give the title compound 372 as a white solid.

15

#### Example 373

Preparation of 2-Amino-N-(2,4,6-trimethylphenyl)-5-pyridinecarboxamide

Compound 373 was prepared by an analogous method as that of 3, except
using 6-aminonicotinic acid to give the title compound 373 as a white
solid.

#### Example 374

Preparation 3-Amino-N-(2,4,6-trimethylphenyl)-4-pyridinecarboxamide

5

Compound 374 was prepared by an analogous method as that of 3, except using 3-amino-4-pyridinecarboxylic acid to give the title compound 374 as a white solid.

10

# Example 375

<u>Preparation 2-Amino-4-methyl-N-(2,4,6-trimethylphenyl)-5-</u> pyrimidinecarboxamide

15 Compound 375 was prepared by an analogous method as that of 3, except using 2-amino-4-methyl-5-pyrimidinecarboxylic acid to give the title compound 375 as a white solid.

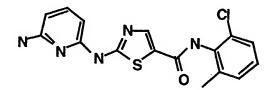
# Example 376

20 <u>Preparation of N-(2-Chloro-6-methylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide</u>

Compound 376 was prepared by an analogous method as that of 319B, except using 2-amino-4-methyl-pyridine to give the title compound 376 as an off-white solid.

## Example 377

<u>Preparation of 2-[(6-Amino-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide</u>



10

5

Compound 377 was prepared by an analogous method as that of 319B, except using 2,6-diaminopyridine to give the title compound 377 as a light brown solid solid.

15

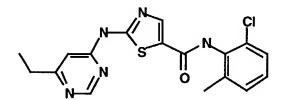
#### Example 378

<u>Preparation of N-(2-Chloro-6-methylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide</u>

Compound 378 was prepared by an analogous method as that of 319B, except using 2-amino-6-propyl-pyridine to give the title compound 378 as an off-white solid.

## Example 379

# Preparation of N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide



10

5

Compound 379 was prepared by an analogous method as that of 319B, except using 4-amino-6-ethyl-pyrimidine to give the title compound 379 as a white solid.

15

#### Examples 380 to 409

#### **General Procedure**

20 Compounds 380 to 409 were prepared by an analogous method as that of 319B. For the following examples 380 to 527 "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 50 mm Ballastic Column, 4 min gradient starting from 100% solvent A

(10% MeOH, 90%  $H_2O$ , 0.2%  $H_3PO_4$ ) to 100% solvent B (90% MeOH, 10%  $H_2O$ , 0.2%  $H_3PO_4$ ), flow rate 4 mL/min,  $\lambda$  = 220 nM. Where used, "HPLC Ret Time B" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 33 mm Turbo Column, 2 min gradient starting from 100% solvent A (10% MeOH, 90%  $H_2O$ , 0.1% TFA) to 100% solvent B (90% MeOH, 10%  $H_2O$ , 0.1% TFA) with 1min at 100% solvent B, flow rate 4 mL/min,  $\lambda$  = 220 nM.

EX.	Compound Structure	Compound Name	HPLC
NO.			Ret Time
000		DY (0.01) 0 (1.1.1.1)	(min)
380		'N-(2-Chloro-6-methylphenyl)-	3.337
	N N S Y Y	2-(2-pyridinylamino)-5-	
	مرد م	thiazolecarboxamide	
381	Q q	'N-(2-Chloro-6-methylphenyl)-	3.61
	HC N N	2-[(6-methyl-2-	
	a <sub>yc</sub>	pyridinyl)amino]-5-	1
		thiazolecarboxamide	
382	<sup>4,C</sup>	'N-(2-Chloro-6-methylphenyl)-	3.487
		2-[(5-methyl-2-	
	high the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of	pyridinyl)aminol-5-	
		thiazolecarboxamide	
383	<b></b>	'N-(2-Chloro-6-methylphenyl)-	3.293
		2-[(4-methyl-2-	
	hyc.	pyridinyl)aminol-5-	
		thiazolecarboxamide	
384	O C	'N-(2-Chloro-6-methylphenyl)-	3.243
	N N S T N T	2-[(3-methyl-2-	
	قبيد 🗪	pyridinyl)aminol-5-	
	- Rr	thiazolecarboxamide	
385	Jos 9	'2-[(5-Bromo-3-methyl-2-	4.17
	what shall	pyridinyl)amino]-N-(2-chloro-6-	
	a <sub>ye</sub> /~	methylphenyl)-5-	
		thiazolecarboxamide	0.015
386		'2-[(6-Amino-2-	2.817
	war in the stand	pyridinyl)aminol-N-(2-chloro-6-	
	Ö <sub>H,C</sub>	methylphenyl)-5-	
	Br	thiazolecarboxamide	
387	7	'2-[(5-Bromo-2-	4.023
	mands Lyng	pyridinyl)aminol-N-(2-chloro-6-	
	ä <sub>ve</sub> /	methylphenyl)-5-	

		thiazolecarboxamide	
388		'N-(2-Chloro-6-methylphenyl)- 2-[[3-(phenylmethoxy)-2- pyridinyl]amino]-5- thiazolecarboxamide 'N-(2-Chloro-6-methylphenyl)- 2-[(5-chloro-2-pyridinyl)amino]-	4.143 3.957
390	H,C N N S N N S N N S N N S N N S N N S N N N S N N N N N N N N N N N N N N N N N N N N	5-thiazolecarboxamide 'N-(2-Chloro-6-methylphenyl)- 2-[(6-ethyl-2-pyridinyl)amino]- 5-thiazolecarboxamide	3.867
391	HC N N S N S	'N-(2-Chloro-6-methylphenyl)- 2-[(6-propyl-2-pyridinyl)amino]- 5-thiazolecarboxamide	4.083
392	H <sub>4</sub> C Br C C C C C C C C C C C C C C C C C C	'2-[(3-Bromo-5-methyl-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide	4.077
393	N N N S N N C C C C C C C C C C C C C C	'2-[(2-Amino-3- pyridinyl)amino]-N-(2-chloro-6- methylphenyl)-5- thiazolecarboxamide	2.343
394	W N S C C C C C C C C C C C C C C C C C C	'2-[(3-Amino-2- pyridinyl)amino]-N-(2-chloro-6- methylphenyl)-5- thiazolecarboxamide	2.777
395	Market Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored Colored	'N-(2-Chloro-6-methylphenyl)- 2-(4-pyridinylamino)-5- thiazolecarboxamide	2.493
396	N J N S J N CO	'N-(2-Chloro-6-methylphenyl)- 2-(3-pyridinylamino)-5- thiazolecarboxamide	2.47
397	CL CL CL CL CL CL CL CL CL CL CL CL CL C	'N-(2-Chloro-6-methylphenyl)- 2-[(6-chloro-3-pyridinyl)amino]- 5-thiazolecarboxamide	3.75
398	S N S N S N S N S N S N S N S N S N S N	'N-(2-Chloro-6-methylphenyl)- 2-[(2-chloro-3-pyridinyl)amino]- 5-thiazolecarboxamide	3.443
399		'N-(2-Chloro-6-methylphenyl)- 2-[(6-methoxy-3- pyridinyl)amino]-5- thiazolecarboxamide	3.517

	Y		
400	The state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the s	'N-(2-Chloro-6-methylphenyl)- 2-[(3,5-dimethyl-2- pyrazinyl)amino]-5- thiazolecarboxamide 'N-(2-Chloro-6-methylphenyl)-	3.697
	N/s / n <sub>uc</sub>	2-(phenylamino)-5- thiazolecarboxamide	
402	HC CI	'N-(2-Chloro-6-methylphenyl)- 2-[(3-ethylphenyl)amino]-5- thiazolecarboxamide	4.107
403	me Control	N-(2-Chloro-6-methylphenyl)- 2-[(3,5-dimethylphenyl)amino]- 5-thiazolecarboxamide	3.98
404	HC-CONSTRUCTION	'N-(2-Chloro-6-methylphenyl)- 2-[(4,6-dimethyl-2- pyrimidinyl)amino]-5- thiazolecarboxamide	3.51
405	H <sub>C</sub> H <sub>C</sub> C	N-(2-Chloro-6-methylphenyl)- 2-[(6-ethyl-4- pyrimidinyl)amino]-5- thiazolecarboxamide	2.943
406		N-(2-Chloro-6-methylphenyl)- 2-[(6-chloro-2-pyrazinyl)amino]- 5-thiazolecarboxamide	3.763
407	HAN SHIP CO	'2-[(3-Aminophenyl)amino]-N- (2-chloro-6-methylphenyl)-5- thiazolecarboxamide	2.633
408	HO S N S S S S S S S S S S S S S S S S S	'N-(2-Chloro-6-methylphenyl)- 2-[(3-hydroxyphenyl)amino]-5- thiazolecarboxamide	3.337
409	B-CINCS MAC	'2-[(3-Bromophenyl)amino]-N- (2-chloro-6-methylphenyl)-5- thiazolecarboxamide	4.12

# Example 410

# $\frac{Preparation\ of\ 'N-(2,6-Dimethylphenyl)-2-(phenylamino)-5-}{thiazolecarboxamide}$

A. [5-[[(2,6-dimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester

5 Compound 410A was prepared by an analogous method as that of 315C, except using 2,6-dimethylaniline.

B. 2-Amino-N-(2,6-dimethylphenyl)- 5-thiazolecarboxamide

Compound 410B was prepared by an analogous method as that of 315D,

except using compound 410A.

#### C. Title Compound

15

The title compound was prepared by an analogous method as that of **319B**, except using compound **410B** and aniline. HPLC Ret. Time 3.69min.

#### **Examples 411 to 427**

#### 20 General Procedure

Compounds 411 to 427 were prepared by an analogous method as that of 319B.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time
NO.			(min)
411	HC PHO CH	'N-(2,6-Dimethylphenyl)-2- (methylphenylamino)-5- thiazolecarboxamide	3.667
412	WINTS HIS	'N-(2,6-Dimethylphenyl)-2-(2-pyridinylamino)-5-thiazolecarboxamide	3.297
413	HC N S HC	'N-(2,6-Dimethylphenyl)-2-[(6-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.587
414		'N-(2,6-Dimethylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.222
415		'N-(2,6-Dimethylphenyl)-2-[(4-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide	3.54
416	HO TO THE	'N-(2,6-Dimethylphenyl)-2- [(4,6-dimethyl-2- pyridinyl)amino]-5- thiazolecarboxamide	3.543
417	HAN NO NO STANDARD	'2-[(6-Amino-2- pyridinyl)amino]-N-(2,6- dimethylphenyl)-5- thiazolecarboxamide	2.807
418	HC N S CHC	'N-(2,6-Dimethylphenyl)-2-[(6- ethyl-2-pyridinyl)amino]-5- thiazolecarboxamide	3.847
419	H,C N N S N S N S N S N S N S N S N S N S	'N-(2,6-Dimethylphenyl)-2-[(6- propyl-2-pyridinyl)amino]-5- thiazolecarboxamide	4.057
420	HA STAGE	'2-[(2-Amino-3- pyridinyl)amino]-N-(2,6- dimethylphenyl)-5- thiazolecarboxamide	2.337
421	N S PLOC	'2-[(3-Amino-2- pyridinyl)amino]-N-(2,6- dimethylphenyl)-5- thiazolecarboxamide	2.737

422	J**	'2-[(6-Amino-2-methyl-4-	2.71
	not I may	pyrimidinyl)amino]-N-(2,6-	
	N N S	dimethylphenyl)-5-	
	<b></b>	thiazolecarboxamide	
423	7	'N-(2,6-Dimethylphenyl)-2-[[6-	2.727
	~~ ~~ ~~ ~~ ~~ ~~ ~~ ~~ ~~ ~~ ~~ ~~ ~~	(4-morpholinyl)-3-	
		pyridazinyl]amino]-5-	
		thiazolecarboxamide	
424	CI HIG	'2-[(6-Chloro-3-	3.46
		pyridazinyl)amino]-N-(2,6-	
	" 's The	dimethylphenyl)-5-	
	,,,,	thiazolecarboxamide	
425	The state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the s	'N-(2,6-Dimethylphenyl)-2-(3-	2.973
		pyridazinylamino)-5-	
	" s ayo	thiazolecarboxamide	
426	H,Ç	'2-[(3-Aminophenyl)amino]-N-	2.63
	HAN	(2,6-dimethylphenyl)-5-	
	" s" ll	thiazolecarboxamide	
427	н <u>.</u> е	'2-[(3-Bromophenyl)amino]-N-	4.143
	Br	(2,6-dimethylphenyl)-5-	
	" 's' hich	thiazolecarboxamide	

# Example 428

Preparation of '2-(2-Pyridinylamino)-N-(2,4,6-trimethylphenyl)-5-

thiazolecarboxamide

A. [5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid,

10 1,1-dimethylethyl ester

5

Compound 428A was prepared by an analogous method as that of 315C, except using 2,4,6-trimethylaniline.

# B. 2-Amino-N-(2,6-dimethylphenyl)- 5-thiazolecarboxamide

Compound 428B was prepared by an analogous method as that of 315D, except using compound 428A.

# 5 <u>C. Title Compound</u>

The title compound was prepared by an analogous method as that of **319B**, except using compound **428B** and 2-aminopyridine. HPLC Ret. Time 3.66min.

10

# Examples 429 to 443

#### 15 General Procedure

Compounds 429 to 443 were prepared by an analogous method as that of 319B.

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
429	HC N N S PHC OH	'2-[(6-Methyl-2-pyridinyl)amino]- N-(2,4,6-trimethylphenyl)-5- thiazolecarboxamide	3.903
430	HC THE ALCON	'2-[(5-Methyl-2-pyridinyl)amino]- N-(2,4,6-trimethylphenyl)-5- thiazolecarboxamide	3.8
431	S. C. C. C. C. C. C. C. C. C. C. C. C. C.	'2-[(4-Methyl-2-pyridinyl)amino]- N-(2,4,6-trimethylphenyl)-5- thiazolecarboxamide	3.603

	T	<del></del>	·
432	Charles Arice Corrections	'2-[(3-Methyl-2-pyridinyl)amino]- N-(2,4,6-trimethylphenyl)-5- thiazolecarboxamide	3.56
433	BT HIGH	'2-[(5-Bromo-2-pyridinyl)amino]- N-(2,4,6-trimethylphenyl)-5- thiazolecarboxamide	4.263
434	a hugh	'2-[(5-Chloro-2-pyridinyl)amino]- N-(2,4,6-trimethylphenyl)-5- thiazolecarboxamide	4.203
435	Pri and a second	'2-[(6-Methoxy-3- pyridinyl)amino]-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	3.8
436	The things	'2-[(4-Ethyl-2-pyridinyl)amino]- N-(2,4,6-trimethylphenyl)-5- thiazolecarboxamide	3.86
437	HC SHIC OH,	'2-[(6-Ethyl-2-pyridinyl)amino]- N-(2,4,6-trimethylphenyl)-5- thiazolecarboxamide	4.127
438	a High	'2-[(6-Chloro-3-pyridinyl)amino]- N-(2,4,6-trimethylphenyl)-5- thiazolecarboxamide	4.017
439	Hotal Age of	'2-[(2,6-Dimethyl-4- pyrimidinyl)amino]-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	2.943
440	or the state of	'2-[(4-Methyl-2- pyrimidinyl)amino]-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	3.723
441	The state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the s	'2-(2-Pyrazinylamino)-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	3.65
442	CH N N S PHIC CH,	'2-[(6-Chloro-2-pyrazinyl)amino]- N-(2,4,6-trimethylphenyl)-5- thiazolecarboxamide	4.05
443	Hyc Charles Hyc Carl	'2-[(3,5-Dimethyl-2- pyrazinyl)amino]-N-(2,4,6- trimethylphenyl)-5- thiazolecarboxamide	3.877

#### Example 444

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide

5

<u>A</u>

$$CI$$
 $N$ 
 $CH_3$ 
 $N$ 
 $H_3C$ 

To a suspension of NaH (148mg, 6.17mmol) in THF (20mL) was added a solution of compound 315D (551mg, 2.06mmol) in THF (10mL) and stirred at RT for 0.5h. A solution of 4,6-dichloro-2-methylpyrimidine (671.6mg, 4.12mmol) in THF (10mL) and stirred at RT overnight. The reaction was quenched with acetic acid and the solvent removed in vacuo. Water and saturated NaHCO<sub>3</sub> were added to the residue and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was removed in vacuo and the crude material purified by column chromatography to give 444A (494mg).

#### B. Title Compound

To compound 444A (30mg) was added N-(2-aminoethyl)-morpholine (300μL) and the mixture was heated at 80°C for 2h. Water was added to the reaction and the product was collected by filtration. HPLC Ret. Time 2.357min.

# Examples 445 to 461

# General Procedure

5 Compounds 445 to 461 were prepared by an analogous method as that of 444B by substituting the appropriate amine.

EX.	Compound Structure	Compound Name	HPLC
NO.			Ret Time
İ			(min)
445	F 19	'N-(2-Chloro-6-methylphenyl)-2-	2.253
		[[2-methyl-6-[[3-(4-	
	" "-" "Hack"	morpholinyl)propyl]amino]-4-	
	,,	pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
446	,	'N-(2-Chloro-6-methylphenyl)-2-[[2-	2 403
110	High Saland	methyl-6-[methyl[3-(methyl-	2.430
	4c   4c   1	amino)propyl]amino]-4-pyrimi-	
	òs,	dinyl]amino]-5-thiazole-	
		carboxamide	
447	~~ ~ a	'N-(2-Chloro-6-methylphenyl)-2-	2.71
		[[2-methyl-6-[[2-(tetrahydro-2-oxo-	
	Hard Buch	1H-imidazol-1-yl)ethyl]-amino]-4-	
	сц	pyri-midinyl]amino]-5-thiazole-	
<u></u>		carboxamide	
448			2.303
		[[2-methyl-6-[(2-1H-imidazol-4-	
	N-Con Herri	ylethyl)amino]-4-	
!		pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
449	γ <b>_</b> γ	N-(2-Chloro-6-methylphenyl)-2-	3.337
		[[2-methyl-6-(4-morpholinyl)-4-	
	The state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the s	pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
450	Ol Chiral	'N-(2-Chloro-6-methylphenyl)-2-	2.703
	5	[[6-[[[(2R)-1-ethyl-2-	
	HC OHC	pyrrolidinyl]methyl]amino]-2-	
	~ ~ ~	methyl-4-pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
451	GI Chiral		2.717
		[[6-[[(2S)-1-ethyl-2-	
	" OHE OHE	pyrrolidinyl]methyl]amino]-2-	
		Fy	

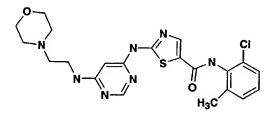
		methyl-4-pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
452	Short hand a cuping	'2-[[6-[(2S)-2-(Aminocarbonyl)-1-	2.81
		pyrrolidinyl]-2-methyl-4-	
	The state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the s	pyrimidinyl]amino]-N-(2-chloro-	
	•	6-methylphenyl)-5-	
		thiazolecarboxamide	
453	но м п	'N-(2-Chloro-6-methylphenyl)-2-	2.677
		[[6-[(2-hydroxyethyl)amino]-2-	
	N-OH HIC	methyl-4-pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
454	n—(1) 8	'N-(2-Chloro-6-methylphenyl)-2-	3.05
		[[6-[4-(hydroxymethyl)-1-	
[	\( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \	piperidinyl]-2-methyl-4-	
		pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
455	, P	'N-(2-Chloro-6-methylphenyl)-2-	2.717
		[[6-[4-(2-hydroxyethyl)-1-	
	HO CH HE	piperazinyl]-2-methyl-4-	
		pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
456	] " [ <sup>*</sup> ] " [	'1-[6-[[5-[[(2-Chloro-6-	2.863
		methylphenyl)amino]carbonyl]-	
	IN WIND HE WE	2-thiazolyl]amino]-2-methyl-4-	
		pyrimidinyl]-4-	
		piperidinecarboxamide	
457	HC 1 C C C C C C C C C C C C C C C C C C	'N-(2-Chloro-6-methylphenyl)-2-	2.823
ĺ		[[2-methyl-6-[(3S)-3-methyl-1-	
	l Day 13c 1	piperazinyl]-4-	
		pyrimidinyl]amino]-5-	
	<u> </u>	thiazolecarboxamide	
<b>458</b>		'2-[[6-[3-(Acetylamino)-1-	2.78
		pyrrolidinyl]-2-methyl-4-	1
	OH, NY	pyrimidinyl]amino]-N-(2-chloro-	
		6-methylphenyl)-5-	
	Nt Nt	thiazolecarboxamide	0.000
459			2.383
		[[6-[[2-(1-methyl-2-	
	or which	pyrrolidinyl)ethyl]amino]-2-	
		methyl-4-pyrimidinyl]amino]-5-	
	M	thiazolecarboxamide	
<b>460</b>		1 ' 3 ' 1	3.027
		[[2-methyl-6-[[(5-methyl-2-	
	the of the	pyrazinyl)methyl]amino]-4-	
		pyrimidinyl]amino]-5-	
		thiazolecarboxamide	

461		'N-(2-Chloro-6-methylphenyl)-2- [[2-methyl-6-[[2-(1H-1,2,3- triazol-1-yl)ethyl]amino]-4- pyrimidinyl]amino]-5- thiazolecarboxamide	2.78
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# Example 462

# Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-

# 5 <u>morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide</u>



<u>A</u>

10

Compound 462A was prepared by an analogous method as that of 444A, except using 4,6-dichloropyrimidine.

## 15 B. Title Compound

The title compound was prepared by an analogous method as that of **444B**, except using compound **462A** in place of compound **444A**. HPLC Ret. Time 2.553min.

20

# Examples 463 to 472

## **General Procedure**

Compounds 463 to 472 were prepared by an analogous method as that of 444B by substituting the appropriate amine. "HPLC Ret Time B" is the HPLC retention time under the following conditions: YMC S5 ODS 4.6 x 33 mm Turbo Column, 2 min gradient starting from 100% solvent A (10% MeOH, 90%  $\rm H_2O$ , 0.1% TFA) to 100% solvent B (90% MeOH, 10%  $\rm H_2O$ , 0.1% TFA) with 1min at 100% solvent B, flow rate 4 mL/min,  $\lambda$  = 220 nM.

EX.	Compound Structure	Compound Name	HPLC
NO.			Ret Time
			(min)
463	"FY Y	'N-(2-Chloro-6-methylphenyl)-	2.527
		2-[[6-[[2-(dimethyl-amino)-	
j	нс	ethyl]amino]-4-pyrimidinyl]-	
		amino]-5-thiazolecarboxamide	
464	المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة المراجعة الم	'N-(2-Chloro-6-methylphenyl)-	2.797
		2-[[6-[[2-(tetrahydro-2-oxo-1H-	
	° 40-	imidazol-1-yl)ethyl]amino]-4-	
		pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
465	*********	'N-(2-Chloro-6-methylphenyl)-	1.137 B
		2-[[6-[methyl[2-(methylamino)-	
	45	ethyl]amino]-4-pyrimidinyl]-	
		amino]-5-thiazolecarboxamide	
466		'N-(2-Chloro-6-methylphenyl)-	1.113 B
	Ta, Ta,	2-[[6-[[2-(1-methyl-2-	
ľ	<b>~</b>	pyrrolidinyl)ethyl]amino]-4-	
		pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
467		'N-(2-Chloro-6-methylphenyl)-	1.150 B
		2-[[6-[[2-(1-pyrrolidinyl)-	
	~~ <del>`</del>	ethyl]amino]-4-pyrimidinyl]-	:
		amino]-5-thiazolecarboxamide	
468	Que sa la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya de la companya della companya della companya de la companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya della companya de	'N-(2-Chloro-6-methylphenyl)-	1.237 B
		2-[[6-[[(1-ethyl-2-pyrrolidinyl-	
	nc-	)methyl]amino]-4-pyrimi-	
		dinyl]amino]-5-thiazole-	
		carboxamide	

469	ann	'N-(2-Chloro-6-methylphenyl)-	1.160	В
		2-[[6-[(4-piperidinyl-		
	no-	methyl)amino]-4-pyrimi-		
		dinyl]amino]-5-thiazole-		
		carboxamide		
470		'2-[[6-[[2-(Acetylamino)-	2.457	В
		ethyl]amino]-4-pyrimi-		
		dinyl]amino]-N-(2-chloro-6-		
		methylphenyl)-5-thiazole-		
		carboxamide		ļ
471		'N-(2-Chloro-6-methylphenyl)-	2.897	
		2-[[6-[[2-(1H-1,2,3-triazol-1-		
	, L	yl)ethyl]amino]-4-		
	Name /	pyrimidinyl]amino]-5-		
		thiazolecarboxamide		
472	N C	'N-(2-Chloro-6-methylphenyl)-	3.437	
		2-[[6-(4-morpholinyl)-4-		
		pyrimidinyl]amino]-5-		
		thiazolecarboxamide		

# Example 473

# Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-

 $\underline{morpholinyl) ethyl] \underline{amino]-2-pyridinyl] \underline{amino]-5-thiazolecarboxamide}$ 

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A.

To a suspension of NaH (2.83g,118mmol) in DMF (350mL) cooled to 0°C was added compound 319A (31g, 93.5mmol). The mixture was stirred for 45min at 0°C then Bu,NI (6.9g, 18.7mmol) was added followed by addition of 4-methoxy benzylchloride (18g, 115mmol). The reaction was allowed to warm to RT. After stirring overnight at RT the reaction was quenched slowly with acetic acid then the solvent removed in vacuo. To the residue was added water and neutralized with saturated aqueous NaHCO<sub>3</sub>. The mixture was extracted 3 times with EtOAc and the combined organic layers washed with water then washed with saturated NaCl solution. The EtOAc layer was concentrated in vacuo and the residue purified by column chromatography to give 473A (35g).

 $\underline{\mathbf{B}}$ 

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To compound 473A (0.5g, 1.1mmol) dissolved in THF (50mL) was slowly added NaH (0.13g, 5.5mmol) followed by 2-bromo-6-aminopyridine (0.76g, 4.4mmol). The reaction was heated to reflux for 2h then cooled to RT and quenched with acetic acid. The solvent was removed in vacuo then water and hexane was added and stirred at RT. The solid precipitate was collected by filtration and washed with water and Et<sub>2</sub>O to give 473B (0.48g)

 $\underline{\mathbf{C}}$ 

To compound 473B (0.48g) dissolved in TFA (5mL) was added anisole (2mL) followed by triflic acid (1mL). The reaction was stirred at RT for 3h then was slowly added to a rapidly stirred mixture of ice, saturated NaHCO<sub>3</sub>, Et<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub>. The mixture was stirred cold for 1h then the solid precipitate was collected by filtration and washed with water followed by Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>mixture to give 473C (0.344g). HPLC Ret. Time 3.85min.

#### D. Title Compound

The title compound was prepared by an analogous method as that of 444B, except using compound 473C in place of compound 444A. HPLC Ret. Time 2.80min.

#### **Examples 474 to 480**

#### General Procedure

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Compounds 474 to 480 were prepared by an analogous method as that of 473D by substituting the appropriate amine.

	Compound Structure	Compound Name	HPLC
NO.			Ret Time
		•	(min)
474		N-(2-Chloro-6-methylphenyl)-	2.867
		2-[[6-[[3-(4-morpholinyl)-	
		propyl]amino]-2-pyridinyl]-	
		amino]-5-thiazolecarboxamide	1

N.	DT (0 CT )	10.00=
HC		3.067
ης <u>~</u> ης ~		j
	pyridinyl]amino]-5-thiazole-	
	carboxamide	
HC N Chiel	'N-(2-Chloro-6-methylphenyl)-	2.827
	2-[[6-[(3S)-3-methyl-1-	
	piperazinyl]-2-pyridinyl]-	
	amino]-5-thiazolecarboxamide	
	'N-(2-Chloro-6-methylphenyl)-	2.83
	2-[[6-[(3-1H-imidazol-1-	
	ylpropyl)amino]-2-pyridinyl]-	
	amino]-5-thiazolecarboxamide	
	'N-(2-Chloro-6-methylphenyl)-	3.077
"S" S"	2-[[6-[(2-hydroxyethyl)amino]-	
" " " " " " " " " " " " " " " " " " "	2-pyridinyl]amino]-5-	
	thiazolecarboxamide	
(h) 1/2 8	'N-(2-Chloro-6-methylphenyl)-	2.903
	2-[[6-[(2-1H-imidazol-1-	
	ylethyl)amino]-2-pyridinyl]-	
	amino]-5-thiazolecarboxamide	
N_ PI	'N-(2-Chloro-6-methylphenyl)-	3.727
	2-{[6-(4-morpholinyl)-2-	
	pyridinyl]amino]-5-	
<b>3</b> -	thiazolecarboxamide	
	/ a U	N-(2-Chloro-6-methylphenyl)- 2-[[6-[(3S)-3-methyl-1- piperazinyl]-2-pyridinyl]- amino]-5-thiazolecarboxamide  N-(2-Chloro-6-methylphenyl)- 2-[[6-[(3-1H-imidazol-1- ylpropyl)amino]-2-pyridinyl]- amino]-5-thiazolecarboxamide  N-(2-Chloro-6-methylphenyl)- 2-[[6-[(2-hydroxyethyl)amino]-5- thiazolecarboxamide  N-(2-Chloro-6-methylphenyl)- 2-[[6-[(2-1H-imidazol-1- ylethyl)amino]-2-pyridinyl]- amino]-5-thiazolecarboxamide  N-(2-Chloro-6-methylphenyl)- 2-[[6-(4-morpholinyl)-2- pyridinyl]amino]-5-

# Example 481

# <u>Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-morpholinyl)ethyl]amino]-2-pyrazinyl]amino]-5-thiazolecarboxamide</u>

5

A.

Compound **481A** was prepared by an analogous method as that of **473B**, except using compound 2-chloro-6-aminopyrazine in place of compound 2-bromo-6-aminopyridine.

# B. (alternate synthesis for compound 406)

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5

Compound 406 was prepared by an analogous method as that of 473C, except using compound 481A in place of compound 473B.

15

## C. Title Compound

The title compound was prepared by an analogous method as that of 444B, except using compound 406 in place of compound 444A. HPLC Ret. Time 2.69min.

20

## Examples 482 to 486

#### General Procedure

5 Compounds 482 to 486 were prepared by an analogous method as that of 481C by substituting the appropriate amine.

EX.	Compound Structure	Compound Name	HPLC
NO.	Compound Surdevare	Compound Ivamo	Ret Time
1.0.			(min)
482		'N-(2-Chloro-6-methylphenyl)-	2.783
		2-[[6-[[3-(4-morpholinyl)-	
	" Ly Ouc	propyl]amino]-2-pyrazinyl]-	
		amino]-5-thiazolecarboxamide	
483	Z C	'N-(2-Chloro-6-methylphenyl)-	3.57
	s s	2-[[6-(4-morpholinyl)-2-	
		pyrazinyl]amino]-5-thiazole-	
		carboxamide	
484	HC N Chiral	N-(2-Chloro-6-methylphenyl)-	2.743
		2-[[6-[(3S)-3-methyl-1-	
	" Ly "Ho	piperazinyl]-2-pyrazinyl]-	
		amino]-5-thiazolecarboxamide	
485	N 0	N-(2-Chloro-6-methylphenyl)-	3.327
	10 / 1 / 5 / 1 / 1 / 1 / 1 / 1 / 1 / 1 / 1	2-[[6-(3-hydroxy-1-	
	O'TO O'TO	pyrrolidinyl)-2-pyrazinyl]-	
		amino]-5-thiazolecarboxamide	
486	N-/ P	'N-(2-Chloro-6-methylphenyl)-	2.68
	N= S-N-	2-[[6-(1H-imidazol-1-yl)-2-	
	l line line	pyrazinyl]amino]-5-	
	•	thiazolecarboxamide	

10 <u>Example 487</u>

<u>Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(3-hydroxy-1-pyrrolidinyl)-3-pyridazinyl]amino]-5-thiazolecarboxamide</u>

A.

5

Compound **487A** was prepared by an analogous method as that of **473B**, except using compound 3-chloro-5-aminopyridazine in place of compound 2-bromo-6-aminopyridine.

10 <u>B</u>

15

Compound 487B was prepared by an analogous method as that of 473C, except using compound 487A in place of compound 473B.

C. Title Compound

The title compound was prepared by an analogous method as that of 444B, except using compound 487B in place of compound 444A, and 3-hydroxypyrrolidine in place of N-(2-aminoethyl)-morpholine. HPLC Ret. Time 2.493min.

5

# Example 488

# <u>Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(1H-imidazol-1-yl)-3-pyridazinyl]amino]-5-thiazolecarboxamide</u>

10

Compound 488 was prepared by an analogous method as that of 487C, except using imidazole in place of 3-hydroxypyrrolidine. HPLC Ret. Time 2.61min.

15

# Example 489

# <u>Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[3-(methylamino)-2-pyrazinyl]amino]-5-thiazolecarboxamide</u>

20

A.

Compound **489A** was prepared by an analogous method as that of **473B**, except using compound 2-chloro-3-aminopyrazine in place of compound 2-bromo-6-aminopyridine.

<u>B</u>

5

Compound 489B was prepared by an analogous method as that of 473C, except using compound 489A in place of compound 473B.

# C. Title Compound

The title compound was prepared by an analogous method as that of 444B, except using compound 489B in place of compound 444A, and using methylamine in place of N-(2-aminoethyl)-morpholine. HPLC Ret. Time 2.81min.

20

# Examples 490 to 494

# General Procedure

5 Compounds **490** to **494** were prepared by an analogous method as that of **489C** by substituting the appropriate amine.

EX.	Compound Structure	Compound Name	HPLC
NO.	•	1	Ret
			Time
			(min)
490	<u> </u>	'N-(2-Chloro-6-methylphenyl)-	2.82
		2-[[3-(3-hydroxy-1-	
		pyrrolidinyl)-2-	
		pyrazinyl]amino]-5-	
		thiazolecarboxamide	
491	P1 P1	'N-(2-Chloro-6-methylphenyl)-	2.94
	s N	2-[[3-(cyclopropylamino)-2-	
		pyrazinyl]amino]-5-	
	·	thiazolecarboxamide	
492	°	'N-(2-Chloro-6-methylphenyl)-	3.643
		2-[[3-(4-morpholinyl)-2-	
		pyrazinyl]amino]-5-	
	•	thiazolecarboxamide	
493	€ N	'N-(2-Chloro-6-methylphenyl)-	2.72
		2-[[3-[[2-(4-	
		morpholinyl)ethyl]amino]-2-	
		pyrazinyl]amino]-5-	
		thiazolecarboxamide	
494	Hc-10°	'2-[[3-[[2-	2.933
		(Acetylamino)ethyl]amino]-2-	
		pyrazinyl]amino]-N-(2-chloro-6-	
	<b>""</b>	methylphenyl)-5-	
		thiazolecarboxamide	

## Example 495

# <u>Preparation of 'N-(2-Chloro-6-methylphenyl)-2-(cyclohexylamino)-5-</u> <u>thiazolecarboxamide</u>

5

Compound **495** was prepared by an analogous method as that of **444B**, except using compound **319A** in place of compound **444A**, and using cyclohexylamine in place of N-(2-aminoethyl)-morpholine. HPLC Ret.

10 Time 3.547min.

# Examples 496 to 500

## 15 General Procedure

Compounds **496** to **500** were prepared by an analogous method as that of **495** by substituting the appropriate amine.

20

EX. NO.	Compound Structure	Compound Name	HPLC Ret Time (min)
496	H,C S H,C CI	'N-(2-Chloro-6-methylphenyl)- 2-(methylamino)-5- thiazolecarboxamide	2.357
497		'N-(2-Chloro-6-methylphenyl)- 2-(cyclopropylamino)-5- thiazolecarboxamide	2.887

498		'N-(2-Chloro-6-methylphenyl)- 2-[(phenylmethyl)amino]-5- thiazolecarboxamide	3.500
499		'2-[[2- (Acetylamino)ethyl]amino]-N- (2-chloro-6-methylphenyl)-5- thiazolecarboxamide	2.483
500	HQ N S N Chreu	'N-(2-Chloro-6-methylphenyl)- 2-[[(1R)-1-(hydroxymethyl)-3- methylbutyl]amino]-5- thiazolecarboxamide	3.407

## Example 501

5 <u>Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(methoxymethyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide</u>

$$\mathsf{H}_3\mathsf{CO} \underbrace{\hspace{1cm} \mathsf{N} \hspace{1cm} \mathsf{N}}_{\mathsf{N} \hspace{1cm} \mathsf{N}} \underbrace{\hspace{1cm} \mathsf{N} \hspace{1cm} \mathsf{N}}_{\mathsf{N} \hspace{1cm} \mathsf{N}} \underbrace{\hspace{1cm} \mathsf{CH}_3}_{\mathsf{CI}}$$

10

Α

To the mixture of methyl 4-methoxyacetoacetate (14.6 g, 0.1 moL) and formami-dine hydrogen chloride salt (16.1 g, 0.2 moL) in 70 mL of dry MeOH was added a 25% solution of sodium methoxide (70 mL, 0.3 moL) in MeOH portionwise. A white precipitate was formed immediately. The reaction mixture was stirred at room temperature for 1.0 hr. Acetic acid

(28.6 mL, 0.5 moL) was added and the reaction mixture was concentrated in vacuo. Water was added to the residue and the mixture was supersaturated with NaCl and extracted with EtOAc (x5). Combined extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to give 8.13 g of compound **501A** as a yellow solid.

 $\mathbf{B}$ 

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The mixture of compound **501A** (5.3 g, 37.8 mmoL) and POCl<sub>3</sub> (40 mL) was heated to reflux for 2.0 hrs. Concentration in vacuo and the residue was poured into a mixture of ice-CH<sub>2</sub>Cl<sub>2</sub>. The pH was adjusted to 6.5 to 7 using concentrated NH<sub>4</sub>OH. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (x3) and combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuo followed by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>-EtOAc: 9:1) on silica gel gave 5.33 g of compound **501B** as a pale yellow oil.

20 C

25

The mixture of compound **501B** (3.2 g, 20 mmoL) and NH<sub>4</sub>OH (50 mL) was heated to 85.C in a pressure tube for 3.0 hrs. After cooled to room temperature, the reaction mixture was concentrated in vacuo and the residue was triturated with ether to give 2.81 g of compound **501C** as a pale yellow solid.

D

$$H_3CO \longrightarrow N \longrightarrow S \longrightarrow N \longrightarrow CH_3$$

5 Compound 501D was prepared from compound 501C by a method analogous to that used for the preparation of compound 473B.

E Title Compound

The title compound was prepared from compound **501D** by a method analogous to that used for the preparation of compound **473C**. HPLC Retention time = 3.25 min.

## Example 502

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(hydroxymethyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide

To a solution of compound 501 (56 mg, 0.144 mmoL) in dry CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) cooled at 0.C was added neat BBr<sub>3</sub> (0.054 mL, 0.574 mmoL). The mixture was stirred for 1.0 hr at ambient temperature. MeOH was added slowly with care at 0.C and the resulting mixture was concentrated in

vacuo. Water was added to the residue and pH was adjusted to 7 with Sat'd NaHCO<sub>3</sub>. The white precipitate was collected by filtration, rinsed with water/ether and dried under high vacuum to give 52 mg of Compound **502** as an off-white solid. HPLC Retention time = 2.84 min.

5

# Example 503

# <u>Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinylmethyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide</u>

10

A

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20

To a suspension of compound 502 (44.2 mg, 0.118 mmoL) in 0.5 mL of dry  $\mathrm{CH_2Cl_2}$  was added thionyl chloride (0.086 mL, 1.18 mmoL). The reaction mixture was stirred for 5.0 hrs. Concentration in vacuo and the residue was azeotropic evaporated with  $\mathrm{CH_2Cl_2}$  to give 56 mg of 503 as an yellow solid.

# B Title Compound

The mixture of compound **503A** (20 mg), morpholine (0.014 mL) and disopropylethyl amine (0.09 mL) in 0.5 mL of dry dioxane was heated to

85.C for 4.0 hrs. Concentration in vacuo followed by flash chromatography ( $CH_2Cl_2$ -MeOH-NH<sub>4</sub>OH: 95:5:0.5) on silica gel gave 15 mg of title compound as an off-white solid. HPLC Retention time = 2.52 min.

5

## Examples 504 to 513

## General Procedure

10 Compounds **504** to **513** were prepared from **503A** by a route analogous to that used for the preparation of **503**. The compounds of these examples have the structure:

EX.	Compound Structure	Compound Name	HPLC
NO.	Compound Siructure	Compound Name	Ret
1.0.			Time
			(min)
504	2	'N-(2-Chloro-6-methylphenyl)-	2.083
	*******	2-[[6-[[[2-	
	٠, ١	(dimethylamino)ethyl]amino]m	
	**()	ethyl]-4-pyrimidinyl]amino]-5-	}
		thiazolecarboxamide	
505	n .	'N-(2-Chloro-6-methylphenyl)-	2.593
300	~~~~~~	2-[[6-[[[2-(4-	1.000
	0	morpholinyl)ethyl]amino]meth	
	#\$ <del>-</del> (_)	yl]-4-pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
506	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	'N-(2-Chloro-6-methylphenyl)-	2.163
		2-[[6-[[[3-(4-	
	nc_	morpholinyl)propyl]amino]met	
	* _	[hyl]-4-pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
507	Immer .	'N-(2-Chloro-6-methylphenyl)-	2.693
		2-[[6-[[[3-(2-oxo-1-	
		pyrrolidinyl)propyl]amino]meth	
	· 🚽	yl]-4-pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
508	Quant	'N-(2-Chloro-6-methylphenyl)-	2.143
	UP	2-[[6-[[(2-1H-imidazol-4-	
'	"HE-	ylethyl)amino]methyl]-4-	
		pyrimidinyl]amino]-5-	
	<u> </u>	thiazolecarboxamide	
509	Mary .	'N-(2-Chloro-6-methylphenyl)-	1.103 B
	710	2-[[6-[[(3-1H-imidazol-1-	
	щс-	ylpropyl)amino]methyl]-4-	
		pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
510	Q.,,,	'N-(2-Chloro-6-methylphenyl)-	1.113 B
		2-[[6-[[[2-(2-	
	NG-	pyridinyl)ethyl]amino]methyl]-	
		4-pyrimidinyl]amino]-5-	
		thiazolecarboxamide	
511	anne	'N-(2-Chloro-6-methylphenyl)-	1.117 B
		2-[[6-[[[2-(3-	
	HC-	pyridinyl)ethyl]amino]methyl]-	
		4-pyrimidinyl]amino]-5-	
		thiazolecarboxamide	

512	**************************************	'1-[[6-[[5-[[(2-Chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-4-pyrimidinyl]methyl]-4-piperidinecarboxamide	1.207	В
513	No.	'2-[[6-[[[2- (Acetylamino)ethyl]amino]meth yl]-4-pyrimidinyl]amino]-N-(2- chloro-6-methylphenyl)-5- thiazolecarboxamide	1.193	В

# Example 514

# Preparation of 'N-(2-Chloro-6-methylphenyl)-2-(2-naphthalenylamino)-5-

# thiazolecarboxamide

10 <u>A</u>

5

Compound 514A was prepared from 473A by an analogous method as that of 473B, except using 2-aminonapthaline in place of 2-bromo-6-aminopyridine.

5

# B. Title Compound

The title compound was prepared by an analogous method as that of 473C, except using compound 514A in place of compound 473B. HPLC Ret. Time 4.11min.

10

# Example 515

# $\frac{Preparation\ of\ 'N-(2-Chloro-6-methylphenyl)-2-(2-quinolinylamino)-5-}{thiazolecarboxamide}$

15

<u>A</u>

20

Compound 515A was prepared from 473A by an analogous method as that of 473B, except using 2-aminoquinoline in place of 2-bromo-6-aminopyridine.

5

## B. Title Compound

The title compound was prepared by an analogous method as that of 473C, except using compound 515A in place of compound 473B. HPLC Ret. Time 3.94min.

10

## Example 516

## $\frac{Preparation\ of\ 'N-(2-Chloro-6-methylphenyl)-2-(3-isoquinolinylamino)-5-}{thiazolecarboxamide}$

15

<u>A</u>

Compound **516A** was prepared from **473A** by an analogous method as that of **473B**, except using 3-aminoisoquinoline in place of 2-bromo-6-aminopyridine.

5

## B. Title Compound

The title compound was prepared by an analogous method as that of 473C, except using compound 516A in place of compound 473B. HPLC Ret. Time 3.94min.

10

## Example 517

## $\frac{Preparation\ of\ 'N-(2-Chloro-6-methylphenyl)-2-(2-quinoxalinylamino)-5-}{thiazolecarboxamide}$

15

A

Compound 517A was prepared from 473A by an analogous method as that of 473B, except using 2-aminoquinoxaline in place of 2-bromo-6-aminopyridine.

5

## B. Title Compound

The title compound was prepared by an analogous method as that of 473C, except using compound 517A in place of compound 473B. HPLC Ret. Time 3.927min.

10

## Example 518

<u>Preparation of 'N-(2-Chloro-6-methylphenyl)-4-methyl-2-[[2-methyl-6-(4-morpholinyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide</u>

$$0 \\ N \\ N \\ CH_3$$

$$0 \\ H_3C$$

15

<u>A</u>

20

Compound 518A was prepared from 144 by an analogous method as that of 319A.

 $\mathbf{B}$ 

Compound 518B was prepared by an analogous method as that of 473A, except using 518A in place of 319A.

5

<u>C</u>

$$CI$$
 $N$ 
 $CH_3$ 
 $CH_3$ 
 $CI$ 
 $CH_3$ 
 $CI$ 
 $CH_3$ 
 $CI$ 

Compound 518C was prepared by an analogous method as that of 473B, except using 518B in place of 473A, and 4-amino-6-chloro-2-methylpyrimidine in place of 2-amino-6-bromopyridine.

 $\underline{\mathbf{D}}$ 

$$CI$$
 $N$ 
 $CH_3$ 
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Compound 518D was prepared by an analogous method as that of 473C, except using 518C in place of 473B.

## E. Title Compound

The title compound was prepared by an analogous method as that of 444B, except using compound 518D in place of compound 444A, and morpholine in place of N-(2-aminoethyl)-morpholine. HPLC Ret. Time 3.397min.

### 10

## Example 519

Preparation of 'N-(2-Chloro-6-methylphenyl)-4-methyl-2-[[2-methyl-6-[[2-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide

15 Compound **519** was prepared by an analogous method as that of **518E**, except using N-(2-aminoethyl)-morpholine in place of morpholine. HPLC Ret. Time 2.493min.

20

## Example 520

Alternative preparation of compound 321

$$H_3C$$
 $N$ 
 $CH_3$ 
 $H_3C$ 
 $H_3C$ 

A

5

Compound 520A was prepared from 2-aminothiazole according to the procedure described in UK Patent Application GB 2323595A.

10 B

15

20

To a solution of compound 520A (480 mg, 4.0 mmoL) in dry THF (10 mL) cooled at -78.C was added a 2.5M solution of n-BuLi (1.68 mL, 4.2 mmoL) in hexane dropwise via a syringe while kept the internal temperature below -75.C. Upon completion of addition, a beige suspension was obtained. The reaction mixture was stirred for 15 min at -78.C. A solution of 2-chloro-6-methyl phenyl isocyanate (0.6 mL, 4.4 mmoL) in 5 mL of dry THF was added and the reaction mixture was stirred for an additional 2.0 hrs at -78.C. Saturated aq. NH<sub>4</sub>Cl solution (10 mL) was added, the mixture was partitioned between EtOAc-water and extracted with EtOAc (x2). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentration in vacuo to give, after recrystalization from EtOAc-hexane, 0.99 g of title compound as a pale yellow crystalline material.

 $\mathbf{C}$ 

5

Compound 520C was prepared by a method analogous to that used for the preparation of compound 473A, using 520B in place of 319A.

10 D

$$H_3C$$
 $N$ 
 $CH_3$ 
 $H_3C$ 
 $H_3C$ 

Compound **520D** was prepared from compound **520C** by a method analogous to that used for the preparation of compound **473B**.

15

## E. Title Compound

Compound 321 was prepared by a method analogous to that used for the preparation of compound 473C.

## Example 521

## $\frac{Preparation\ of\ '2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-phenyl-5-}{thiazolecarboxamide}$

5

Α

10

Compound **521A** was prepared by an analogous method as that of **520B**, except using phenylisocyanate in place of 2-chloro-6-methylphenylisocyanate.

15

В

Compound **521B** was prepared by a method analogous to that used for the preparation of compound **473A**, using **521A** in place of **319A**.

 $\mathbf{C}$ 

$$H_3C$$
 $N$ 
 $CH_3$ 

5 Compound **521C** was prepared from compound **521B** by a method analogous to that used for the preparation of compound **473B**.

## D Title Compound

10

The title compound was prepared by a method analogous to that used for the preparation of compound 473C. HPLC Ret. Time 1.3 min method B

15

## Example 522

 $\frac{Preparation\ of\ '2\text{-}[(2,6\text{-}Dimethyl\text{-}4\text{-}pyrimidinyl)}\text{methylaminol-}N\text{-}(2\text{-}methylphenyl)\text{-}5\text{-}thiazolecarboxamide}}{\text{methylphenyl})\text{-}5\text{-}thiazolecarboxamide}$ 

20

Α

Compound **522A** was prepared by an analogous method as that of **520B**, except using 2-methylphenylisocyanate in place of 2-chloro-6-

5 methylphenylisocyanate.

В

10

Compound 522B was prepared by a method analogous to that used for the preparation of compound 473A, using 522A in place of 319A.

15 C

$$H_3C$$
 $N$ 
 $CH_3$ 
 $H_3C$ 
 $H_3C$ 

Compound **522C** was prepared from compound **522B** by a method analogous to that used for the preparation of compound **473B**.

D

$$H_3C$$
 $N$ 
 $N$ 
 $O$ 
 $H_3C$ 
 $N$ 
 $O$ 
 $H_3C$ 

5 Sodium hydride (60% in oil; 40 mg; 1 mmol) was added to a solution of compound 522C (280 mg; 0.61 mmol) in 2 ml of DMF at room temp. After stirring 30 minutes, iodomethane (0.2 ml; 3 mmol) was added and the reaction was stirred 4 hr. After the reaction mixture was partitioned between ethyl acetate (50 ml) and water (50 ml), the organic layer was washed with water (2 x 50 ml) and brine (50 ml). Drying (MgSO₄) and concentration afforded an oil that was chromatographed on a 2.5 x 15 cm silica gel column using 50-75% ethyl acetate/hexane. The pure fractions were concentrated and the residue was crystalized from ethyl acetate/hexane to afford 100 mg of 522D as a light yellow solid.

15

## E Title Compound

The title compound was prepared by a method analogous to that used for the preparation of compound 473C. HPLC Ret. Time 1.21 min method B

20

## Example 523

<u>Preparation of '2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-(2-methylphenyl)-5-thiazolecarboxamide</u>

Compound **523** was prepared by a method analogous to that used for the preparation of compound **473C**, except using compound **522C** in place of **473B**. HPLC Ret. Time 1.24 min method B

5

## Example 524

## <u>Preparation of 'N-(3,5-Dimethoxyphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide</u>

10

Α

15

Compound **524A** was prepared by an analogous method as that of **520B**, except using 3,5-dimethoxyphenylisocyanate in place of 2-chloro-6-methylphenylisocyanate.

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 $\mathbf{B}$ 

5 Compound 524B was prepared by a method analogous to that used for the preparation of compound 473A, using 524A in place of 319A.

C

$$H_3C$$
 $N$ 
 $CH_3$ 
 $H_3C$ 
 $O$ 
 $CH_3$ 

10

Compound **524C** was prepared from compound **524B** by a method analogous to that used for the preparation of compound **473B**.

15

20

## D Title Compound

The title compound was prepared by a method analogous to that used for the preparation of compound 473C, except using compound 524C in place of compound 473B HPLC Ret. Time 1.28 min method B

## Example 525

5 <u>Preparation of 'N-[2,6-Bis(1-methylethyl)phenyl]-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide</u>

10 A

Compound **525A** was prepared by an analogous method as that of **520B**,

except using 2,2-diisopropylphenylisocyanate in place of 2-chloro-6methylphenylisocyanate.

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В

5 Compound **525B** was prepared by a method analogous to that used for the preparation of compound **473A**, using **525A** in place of **319A**.

 $\mathbf{C}$ 

10

Compound **525C** was prepared from compound **525B** by a method analogous to that used for the preparation of compound **473B**.

15

D Title Compound

The title compound was prepared by a method analogous to that used for the preparation of compound 473C, except using compound 525C in place of compound 473B. HPLC Ret. Time 1.6 min method B

5

## Example 526

## <u>Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)methylamino]-5-thiazolecarboxamide</u>

10

15

A mixture of compound 321 (110 mg; 0.29 mmol), potassium carbonate (138 mg; 1 mmol) and iodomethane (0.06 ml; 1 mmol) in DMF was stirred 2 hr at room temperature. After the reaction mixture was partitioned between ethyl acetate (25 ml) and water (25 ml), the organic layer was washed with water (2 x 25 ml) and brine (25 ml). Drying (MgSO<sub>4</sub>) and concentration afforded an oil that was chromatographed on a 2.5 x 15 cm silica gel column using 1-4% MeOH/CH<sub>2</sub>Cl<sub>2</sub> and the fractions containing compound 526 were collected to give 20mg of product. HPLC Ret. Time 1.3min method B.

20

## Example 527

<u>Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)aminol-N-methyl-5-thiazolecarboxamide</u>

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Compound 527 was prepared by a method analogous to that used for the preparation of compound 526, except the fractions containing compound 527 were collected to give 60mg of product. HPLC Ret. Time 1.23 min method B

5

10

## Example 528

Preparation of 2-Bromo-N-, N-(2-chloro-6-methylphenyl)-(4-methoxybenzyl)-5-thiazolecarboxamide

To a cooled (0 °C) THF solution of 2-chloro-6-methyl aniline (2.86 mL, 23.3 mmol, 1.10 equiv) was added dropwise a 1.0 M solution of lithium

15 bis(trimethylsilyl)amide (42.2 mL, 42.2 mmol, 2.00 equiv) via syringe.

The homogeneous solution was allowed to stir for 5 minutes, and then a

THF solution of ethyl 2-bromo-5-thiazolecarboxylate (5.00 g, 21.1 mmol,
1.00 equiv, prepared in a manner analogous to compound 319A) was

added via cannula. The solution was allowed to stir for 15 minutes until

20 TLC analysis showed no remaining starting material. To the reaction was
then added 4-methoxybenzyl chloride (7.15 mL, 52.7 mmol, 2.5 equiv),
followed by a catalytic amount of tetrabutylammonium iodide (1.56 g, 4.22
mmol, 0.20 equiv). The homogeneous mixture was allowed to stir
overnight at ambient temperature and then concentrated in vacuo. The

residue was partitioned between ethyl acetate and water, and the organic extracts were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and removal of solvent, the product was purified by flash chromatography (10-20% ethyl acetate in hexanes) to afford the title compound as a tan solid (47%).

## Example 529

Preparation of N-, N-(2-Chloro-6-methylphenyl)-(4-methoxybenzyl)-2-[(6-bromo-2-pyridinyl)amino]-5-thiazolecarboxamide

10

15

5

Compound **529** was prepared in an analogous manner to **319B**, except using **528** and 6-bromo-2-aminopyridine as the reactants.

### Example 530

Preparation of N-(2-Chloro-6-methylphenyl)-2-[(6-bromo-

2-pyridinyl)amino]-5-thiazolecarboxamide

Compound **529** (0.500 g, 0.919 mmol, 1.00 equiv) was dissolved in 5 mL trifluoroacetic acid and charged at ambient temperature with 2 mL anisole followed by 1 mL trifluoromethanesulfonic acid. The dark red homogeneous solution was allowed to stir overnight, and then quenched by carefully pouring the solution into an ice/sodium bicarbonate mixture. A white solid was filtered off and washed sequentially with water, 1:1 hexane/ether, and ether to afford the title compound (41%).

25

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## Examples 531-538

## General Procedure

10

Compounds 531 to 538 were prepared to the general procedure described below. A 1-dram vial was charged with 530 and excess amine and heated 5 to 90 °C overnight. The residue was then purified by reverse phase HPLC to afford the pure compound. For the following examples 531 to 555 "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC ODS-A C18 S7 3.0 x 50 mm, 2 min gradient starting from 100% solvent A (10% MeOH, 90%  $H_{\scriptscriptstyle 2}O,\,0.1\%$  TFA ) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.1% TFA), flow rate 5 mL/min,  $\lambda = 220$  nM.

Compound Structure	Compound Name	HPLC Ret time (min)
	'N-(2-Chloro-6-	1.56
	methylphenyl)-2-[[6-[4-	
	(2-furanylcarbonyl)-1-	
,		
<u>.                                    </u>		1.41
	Benzimidazol-1-	
	yl)propyl]amino]-2-	
م ک	pyridinyl]amino]-N-(2-	Ī
	chloro-6-	
		1.24
	-	1.24
	¥ <u>=</u> ¥	
	pyridinyl]amino]-5-	
	thiazolecarboxamide	
	•	1.25
	1	
	-	'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-furanylcarbonyl)-1-piperazinyl]-2-pyridinyl]amino]-5-thiazolecarboxamide  '2-[[6-[[3-(1H-Benzimidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide  'N-(2-Chloro-6-methylphenyl)-2-[[6-[[4-(1H-imidazol-1-yl)butyl]amino]-2-pyridinyl]amino]-2-pyridinyl]amino]-5-

	<del></del>	1	<del>,                                      </del>
1		thiazolecarboxamide	
535	·	'N-(2-Chloro-6-	1.14
		methylphenyl)-2-[[6-	
		[[3-(4-methyl-1-	
	l the o	piperazinyl)propyl]ami	
		no]-2-	
		pyridinyl]amino]-5-	
		thiazolecarboxamide	
536		'N-(2-Chloro-6-	1.29
		methylphenyl)-2-[[6-	
	andi	[[4-(1H-imidazol-1-	
	N N N S NC	yl)phenyl]amino]-2-	
	•	pyridinyl]amino]-5-	}
		thiazolecarboxamide	
537		'N-(2-Chloro-6-	1.27
	I Dans	methylphenyl)-2-[[6-	
		[[6-(1H-imidazol-1-	
		yl)hexyl]amino]-2-	
		pyridinyl]amino]-5-	
		thiazolecarboxamide	
538		'N-(2-Chloro-6-	1.24
]		methylphenyl)-2-[[6-	
		[(3-1H-imidazol-1-	
	•	ylpropyl)amino]-2-	
		pyridinyl]amino]-5-	
		thiazolecarboxamide	

## Example 539

## Preparation of Ethyl-2-[(6-bromo-2-pyridinyl)amino]-5-thiazolecarboxylate

$$\mathsf{Br} \overset{\mathsf{N}}{ \underset{\mathsf{H}}{ }} \overset{\mathsf{N}}{\underset{\mathsf{S}}{ }} \overset{\mathsf{OEt}}{ }$$

5

Compound **539** was prepared in an analogous manner to **319B**, except using ethyl 2-bromo-5-thiazolecarboxylate and 6-bromo-2-aminopyridine as the reactants.

## Examples 540-550

## General Procedure

Compounds 540 to 550 were prepared according to the general procedure described below. Compound 539 was condensed with the appropriate

5 aniline according to the procedure for example 528 to afford the afford the corresponding N-(4-methoxybenzyl)amide. The intermediate bromopyridine was then reacted with N-(3-aminopropyl)-imidazole according to the procedure for examples 531 to 538 to afford the corresponding diaminopyridine. Removal of the 4-methoxybenzyl group

10 according to the procedure described for example 530 followed by purification by reverse phase preparative HPLC afforded compounds 540 to 550.

EX. NO.	Compound Structure	Compound Name	HPLC Ret time (min)
540		'2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(4-methoxyphenyl)-5-thiazolecarboxamide	1.12
541	o-aploo	'2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(4-phenoxyphenyl)-5-thiazolecarboxamide	1.48
542		'N-(4-Chlorophenyl)-2- [[6-[[3-(1H-imidazol-1- yl)propyl]amino]-2- pyridinyl]amino]-5- thiazolecarboxamide	1.31
543		'2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-[1-(phenylmethyl)-1H-indazol-5-yl]-5-thiazolecarboxamide	1.34

544	'N-(2-Ethylphenyl)-2- [[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2- pyridinyl]amino]-5- thiazolecarboxamide	1.18
545	'N-(2,6- Dimethoxyphenyl)-2- [[6-[[3-(1H-imidazol-1- yl)propyl]amino]-2- pyridinyl]amino]-5- thiazolecarboxamide	1.11
546	'N-(2,4- Dimethoxyphenyl)-2- [[6-[[3-(1H-imidazol-1- yl)propyl]amino]-2- pyridinyl]amino]-5- thiazolecarboxamide	1.06
547	'2-[[6-[[3-(1H-Imidazol- 1-yl)propyl]amino]-2- pyridinyl]amino]-N- phenyl-5- thiazolecarboxamide	1.06
548	'2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(2-methylphenyl)-5-thiazolecarboxamide	1.11
549	'N-(2-Chlorophenyl)-2- [[6-[[3-(1H-imidazol-1- yl)propyl]amino]-2- pyridinyl]amino]-5- thiazolecarboxamide	1.16
550	'N-(2,6-Diethylphenyl)- 2-[[6-[[3-(1H-imidazol- 1-yl)propyl]amino]-2- pyridinyl]amino]-5- thiazolecarboxamide	1.29

Example 551

Preparation of Ethyl-2-[(6-bromo-2-pyridinyl)amino]4-methyl-5-thiazolecarboxylate

Compound **551** was prepared in an analogous manner to **319B**, except using ethyl 2-bromo-4-methyl-5-thiazolecarboxylate and 6-bromo-2-aminopyridine as the reactants.

5

10

## Examples 552 and 553

Compounds **552** and **553** were prepared using a similar procedure described for the preparation of compounds **540** to **550**, except using compound **551** as the starting material.

EX. NO.	Compound Structure	Compound Name	HPLC Ret time (min)
552		'N-(2-Chloro-6- methylphenyl)-2-[[6- [[3-(1H-imidazol-1- yl)propyl]amino]-2- pyridinyl]amino]-4- methyl-5- thiazolecarboxamide	1.19
553		'2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-4-methyl-N-[1-(phenylmethyl)-1H-indazol-5-yl]-5-thiazolecarboxamide	1.35

## Example 554

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[3-[[3-(1H-imidazol-1-yl)propyl]amino]phenyl]amino]-5-thiazolecarboxamide

A solution of **528** (0.127 g, 0.281 mmol, 1.00 equiv) and 3-[N-,N-(tert-butoxycarbonyl)-(3-aminopropyl)-imidazoyl]-1,3-phenylenediamine (0.178 g, 0.563 mmol, 2.00 equiv) in 0.200 mL DMSO was heated at 120 °C in a sealed vial overnight. Purification by reverse phase preparative HPLC followed by deprotection according to the procedure for compound **530** afforded the title compound.

## Example 555

Preparation of 'N-(2-Chloro-6-methylphenyl)-2-[[5-[[3-(1H-imidazol-1-yl)propyl]amino]-2-nitrophenyl]amino]-5-thiazolecarboxamide

A solution of 2,4-difluoronitrobenzene (0.400 mL, 3.65 mmol, 1.00 equiv) in acetonitrile was charged with K<sub>2</sub>CO<sub>3</sub> (0.605 g, 4.38 mmol, 1.20 equiv) followed by ethyl-2-amino-5-thiazolecarboxylate (0.628 g, 3.65 mmol, 1.00 equiv) as a solid. The heterogeneous mixture was sealed and heated to 120 °C overnight. The solution was filtered and then concentrated in vacuo. Purification by flash chromatography afforded ethyl-2-[(3-fluoro-6-nitro-1-phenyl)amino]-

5-thiazolecarboxylate as a yellow solid (9%). This intermediate was coupled with 2-chloro-6-methyl aniline according to the procedure for compound 528 to afford N-(2-Chloro-6-methylphenyl)-2-[3-(fluoro-6-nitro-1-phenyl)amino]-5-thiazolecarboxamide (21%). The title compound was synthesized by reacting this intermediate with excess N-(3-aminopropyl)-imidazole at 80 °C followed by purification by reverse phase preparative HPLC.

## Examples 556-566

## General Procedure:

Compounds 556 to 566 were prepared according to the general procedure described below. A mixture of 2-bromo-N-[2-chloro-6-methylphenyl]-5thiazolecarboxamide 319A, an aniline (1 eq), 1.0 N aqueous HCl (0.5 eq) in n-BuOH was heated overnight at 120°C in a sealed vial. This was 5 diluted with methanol and the product was isolated by preparative HPLC (YMC S5 ODS 30 x 100 mm column eluted with a gradient comprised of two solvent mixtures (mixture A: 10% MeOH, 90% water, and 0.1% TFA; mixture B: 90% MeOH, 10% water, and 0.1% TFA). For anilines substituted with a carboxylic acid group, the reaction mixture was treated 10 with 1 N aqueous NaOH (5 eq) overnight before final purification of the product by HPLC. "HPLC Ret Time" is the HPLC retention time under the following conditions: YMC S5 OSD 4.6 x 30 mm (for 556 to 560) or YMC S7 ODS 3 x 50 mm column (for 561 to 566), 2 min gradient starting from 15 100% solvent A (10% MeOH, 90% H<sub>2</sub>O, 0.1% TFA) to 100% solvent B (90% MeOH, 10% H<sub>2</sub>O, 0.1% TFA), flow rate 5 mL/min,  $\lambda = 220$  nM.

EX. NO.	Compound Structure	Compound Name	HPLC Ret time (min)
556	MeO H S CI	N-(2-Chloro-6- methylphenyl)-2- [(3,4,5-trimethoxy- phenyl)amino]-5- thiazolecarboxamide	1.63

	<del></del>	<del></del>	Υ
557	MeO N S CI	N-(2-Chloro-6-methyl-phenyl)-2-[(4-methoxy-phenyl)amino]-5-thiazolecarboxamide	1.63
558	Meo N S N S N S N S N S N S N S N S N S N	N-(2-Chloro-6-methyl-phenyl)-2-[(3-methoxy-phenyl)amino]-5-thiazolecarboxamide	1.70
559	MeO H S CI	N-(2-Chloro-6-methyl- phenyl)-2-[(2-methoxy- phenyl)amino]-5- thiazolecarboxamide	1.65
560	MeO N N N N N N N N N N N N N N N N N N N	N-(2-Chloro-6-methyl- phenyl)-2-[(3,5- dimethoxyphenyl)- amino]-5- thiazolecarboxamide	1.55
561	N N N N CI	N-(2-Chloro-6-methyl- phenyl)-2-[[4- (dimethylamino)- phenyl]amino]-5- thiazolecarboxamide	1.25
562		N-(2-Chloro-6- methylphenyl)-2-[[4- (4-morpholinyl)phenyl] amino]-5- thiazolecarboxamide	1.24
563	HOSC STATES	N-(2-Chloro-6- methylphenyl)-2-[[3- (carboxymethyl)- phenyl]amino]-5- thiazolecarboxamide	1.36
564	HO <sup>2</sup> C CI	N-(2-Chloro-6- methylphenyl)-2-[[3-(3- carboxypropyl)- phenyl]amino]-5- thiazolecarboxamide	1.48
565	HO <sub>2</sub> C \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	N-(2-Chloro-6- methylphenyl)-2-[[4- (carboxymethyl)phenyl ]amino]-5- thiazolecarboxamide	1.35

566	N N I CO	N-(2-Chloro-6-	1.27
		methylphenyl)-2-[(2- methyl-1H-	
		benzimidazol-5-	
		yl)amino]-5-	
		thiazolecarboxamide	

## Example 567

# $\underline{\text{N-}(2\text{-}Chloro-6\text{-}methylphenyl)-2\text{-}[[1\text{-}[3\text{-}(1H\text{-}imidazol\text{-}1\text{-}yl)propyl]-1}H\text{-}\\\\ \underline{\text{benzimidazol-4-yl]amino]-5\text{-}thiazolecarboxamide}}$

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A mixture of 1-bromo-3-chloropropane (10 mL, 0.10 mmole), imidazole (6.81 gm, 0.10 mmole) in ethanolic NaOEt (41.3 mL, 21 wt%, 1.1 mmole) was heated at reflux for 1 hr. After cooling to RT, this was filtered and the filter cake was washed with EtOH. The solvent was removed from the filtrate to afford crude 3-chloro-1-(imidazo-1-yl)-propane as an oil. A portion of the crude chloride (1.07 gm, 7.40 mmole) was added to a mixture of 4-nitro-benzimidazole (1.09 gm, 6.66 mmole) and NaH (293 mg, 60% in oil, 8.14 mmole) in DMF (15 mL). After being heated at 60°C overnight and then 75°C for 3 hr, the solvent was removed. The residue was partitioned between water and a mixture of 10% MeOH in DCM. The organic phase was separated, dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvents removed. Radial chromatography (4 mm silica gel plate that was eluted with a step gradient of DCM containing 2, 3, 4, ...10% MeOH) afforded the

major product, 1-[3-imidazo-1-ylpropyl]-4-nitro-benzimidazole as a solid (513 mg, 28%). A mixture of this material (250 mg) and 10% palladium on charcoal (200 mg) in EtOH (10 mL) under a hydrogen atmosphere (balloon) was vigorously stirred for 1 hr. Removal of the catalyst by filtration and the solvent under reduced pressure left the crude 4-amino-1-[3-imidazo-1-ylpropyl]-benzimidazole as a solid. A portion of this material (46 mg, 0.191 mmole) was added to a mixture of 319A (63 mg, 1.0 eq), an aqueous solution of HCl (0.24 mL, 1.0 M, 1.25 eq) and n-BuOH (1 mL). This was heated in a sealed vial at 120°C for 44 hr. After cooling to RT, 567 (HPLC retention time (YMC ODS S5 4.6 x 30 mm): 1.20 min) was isolated by preparative HPLC.

## Example 568

N-(2-Chloro-6-methylphenyl)-2-[[1-[2-(1H-imidazol-1-yl)ethyl]-1H-indazol-

6-yl]amino]-5-thiazolecarboxamide

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A mixture of 1-bromo-2-chloroethane (4.6 mL, 0.055 mole), imidazole (3.40 gm, 0.050 mole) in ethanolic NaOEt (19 mL, 21 wt%, 1 eq) was heated at reflux for 2 hr. After cooling to RT, the reaction was filtered and the filter cake was washed with EtOH. The solvent was removed from the filtrate to afford crude 2-chloro-1-(imidazo-1-yl)-ethane. A portion of the crude

chloride (2.24 gm, 17.2 mmole) was added to a mixture of 6-nitro-indazole (1.63 gm, 10.0 mmole), K<sub>2</sub>CO<sub>3</sub> (1.50 mg, 1.1 eq), and KI (1.70 gm, 1.1 eq) in DMF (15 mL). After being heated at 70°C overnight and then 90°C for 4 hr, the solvent was removed. The residue was partitioned between water and a mixture of 5% MeOH in DCM. The organic phase was separated, 5 dried (Na SO,) and the solvents removed. Radial chromatography (4mm silica gel plate that was eluted with a step gradient of DCM containing 0, 1. 2% MeOH) afforded 659 mg of 1-[2-imidazo-1-ylethyl]-6-nitro-indazole and 450 mg of the isomeric 2-[2-imidazo-1-ylethyl]-6-nitro-indazole. A 10 mixture of 1-[2-imidazo-1-ylethyl]-6-nitro-indazole (650 mg) and 10% palladium on charcoal (600 mg) in EtOH (10 mL) under a hydrogen atmosphere (balloon) was vigorously stirred overnight. Removal of the catalyst by filtration and the solvent under reduced pressure left the crude 6-amino-1-[2-imidazo-1-ylethyl]-indazole as a solid. A portion of this material (68.1 mg, 1.5 eq) was added to a mixture of 556 (99.3 mg, 0.300 15 mmole), an aqueous solution of HCl (0.45 mL, 1.0 M, 1.5 eq) and n-BuOH (1.5 mL). This was heated in a sealed vial at 120°C for 44 hr. After cooling to RT, 568 (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.31 min) was isolated by preparative HPLC.

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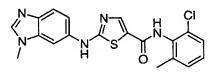
## Example 569

N-(2-Chloro-6-methylphenyl)-2-[[2-[2-(1H-imidazol-1-yl)ethyl]-2H-indazol-6-yl]amino]-5-thiazolecarboxamide

Beginning with the isomeric 2-[2-imidazo-1-ylethyl]-6-nitro-indazole, 569 (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.28 min) was prepared in the same manner as 568.

## Example 570

# $\frac{\text{N-}(2\text{-}Chloro-6-methylphenyl)-2-[(1\text{-}methyl-1H-benzimidazol-6-yl)amino]-5-}{\text{thiazolecarboxamide}}$



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### and

## Example 571

# $\underline{\text{N-}(2\text{-}Chloro-6\text{-}methylphenyl)-}2\text{-}[(1\text{-}methyl-1H\text{-}benzimidazol-}5\text{-}yl)amino]-}5\text{-}$ thiazolecarboxamide

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Beginning with 5-nitrobenzimidazole and methyl iodide, 570 (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.23 min) and 571 (HPLC

retention time (YMC ODS S7 3 x 50 mm): 1.23 min) were prepared in the same manner as compounds 557 and 558.

## Example 572

5 N-(2-Chloro-6-methylphenyl)-2-[[2-[3-(1H-imidazol-1-yl)propyllamino]-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide

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A mixture of 2-chloro-5-nitro-benzimidazole (985 mg, 5.0 mmole) and 1-(3-aminopropyl)-imidazole (1.8 mL, 3 eq) in toluene (15 mL) was heated at reflux for 5 hr. The reaction was partitioned between EtOAc and brine to give a precipitate that was collected by filtration. Flash chromatography of this material (silica gel; stepwise gradient elution with mixtures of DCM containing 1, 2, 3,...10% MeOH) afforded 2-[3-[imidazo-1-yl]-propylamino]-5-nitro-benzimidazole (550mg) as a solid. This material was combined with 10% Pd on charcoal (500 mg), suspended in EtOH, and stirred under a hydrogen atmosphere (balloon) overnight. Removal of the catalyst by filtration and the solvent under reduced pressure left the crude 5-amino-2-[3-imidazo-1-ylpropylamino]- benzimidazole as a solid. A portion of this material (77 mg, 0.30 mmole) was added to a mixture of 319A (99 mg, 1.0 eq), an aqueous solution of HCl (0.60 mL, 1.0 M, 2 eq) and n-BuOH (1.5 mL). This was heated in a sealed vial at 120°C for 20

hr. After cooling to RT, **572** (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.20 min) was isolated by preparative HPLC.

## Example 573

N-(2-Chloro-6-methylphenyl)-2-[[2-(4-morpholinylmethyl)-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide

5

A mixture of 3,4-diamino-nitrobenzene (15.3 g, 0.10 mole) and chloroacetic acid (14.18 gm, 1.5 eq) in 5.0 N aqueous HCl (80 mL) was heated at reflux 10 for 1 hr. After cooling to RT, the reaction was filtered through celite and the filtrate was stored at 0°C for 2 days. The crystals that formed, were collected and recrystallized from a mixture of EtOH and water to give 7.2 gm of the hydrogen chloride salt of 2-chloromethyl-5-nitro-benzimidazole. A portion of this salt (528 mg, 2.13 mmole) and morpholine (1.31 mL, 7 eq) 15 in toluene (15 mL) were heated at reflux for 4 hr. After cooling to RT, the reaction was filtered and the filter cake was washed with toluene. The solvent was removed from the filtrate to leave the crude 2-[Nmorpholinylmethyl]-5-nitro-benzimidazole as an oil. A portion of this material (657 mg) and 10% palladium on charcoal (650 mg) in EtOH (10 20 mL) was stirred overnight under a hydrogen atmosphere (balloon). Removal of the catalyst by filtration and the solvent left the crude 5-

amino-2-[N-morpholinylmethyl]-benzimidazole as an oil. A portion of this material was coupled with **556** as described for **570** to afford **573** (HPLC retention time (YMC ODS S7 3 x 50 mm): 0.92 min).

5 <u>Example 574</u>

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N-(2-Chloro-6-methylphenyl)-2-[[2-(1H-imidazol-1-ylmethyl)-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide

Beginning with imidazole and 2-chloromethyl-5-nitro-benzimidazole

compound 574 (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.17 min)

was prepared in the same manner as compounds 570.

## Example 575

 $\underline{N\text{-}(2\text{-}Chloro\text{-}6\text{-}methylphenyl)\text{-}2\text{-}[[3\text{-}[[5\text{-}(1H\text{-}imidazol\text{-}1\text{-}yl)\text{-}2\text{-}$ 

pyridinyllamino]phenyllamino]-5-thiazolecarboxamide

A mixture of 3-nitroaniline (2.91 gm, 21.1 mmole) and 2,5dibromopyridine (5.0 gm, 1 eq) was heated at 185°C for 1 hr. After cooling

to RT, the solid was broken up and treated with a mixture of saturated aq. NaHCO<sub>3</sub> and 10% MeOH in DCM. The suspended solid was collected by filtration and washed with a little 10% MeOH in DCM and then water to leave, after drying, 3.72 gm of crude N-[5-bromo-pyridin-2-yl]-5
5 nitroaniline. A portion of this material (500 mg, 1.70 mmole) was combined with imidazole (116 mg, 1 eq), CuI (81 mg, 0.25 eq), and K<sub>2</sub>CO<sub>3</sub> (235 mg, 1 eq) in DMF (2 mL) and the mixture was heated at 130°C for 2 days. After cooling to RT, the solvent was removed and the residue was partitioned between water and a mixture of 20% MeOH in DCM. The organic phase was removed, dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvents removed to leave the crude N-[5-imidazo-1-yl]-pyridin-2-yl]-5-nitroaniline as a solid. This was taken and treated with 10% palladium on charcoal (650 mg) in EtOH under a hydrogen atmosphere for 1.5 hr. Removal of the catalyst

aminoaniline. It was purified by radial chromatography (4 mm silica gel plate that was eluted with a step gradient of DCM containing 1, 2, 3,...6% MeOH). The aniline was then coupled with 319A as described for 570 to afford 575 (HPLC retention time (YMC ODS S5 4.6 x 30 mm): 1.42 min).

and then the solvent left the crude N-[5-imidazo-1-yl]-pyridin-2-yl]-5-

## Example 576

20 N-(2-Chloro-6-methylphenyl)-2-[[3-[3-(1H-imidazol-1-yl)propoxy]phenyl]amino]-5-thiazolecarboxamide

and

## Example 577

# N-(2-Chloro-6-methylphenyl)-2-[[4-[3-(1H-imidazol-1-yl)propoxy]phenyl]amino]-5-thiazolecarboxamide

N S N CI

5

A suspension of 3-nitrophenol (837 mg, 6.02 mmole), 1-chloro-3-[imidazo-1-yl]-propane (871 mg, 1 eq), K,CO<sub>3</sub> (3.3 gm, 4 eq) and NaI (1.0 gm, 1.1 eq) in DMF was heated at 120°C for 6 hr. After cooling to RT, the reaction was filtered and the filter cake was washed with DMF. The solvent was removed from the filtrate and the residue was chromatographed (radial 10 chromatography; 4 mm silica gel plate that was eluted with a step gradient of DCM containing 0, 1, 2.5, 5, 7.5% MeOH) to afford 400 mg of 3-[3-imidazo-1-ylpropyloxy]]- nitrobenzene. This was treated with 10% palladium on charcoal (400 mg) in EtOH under a hydrogen atmosphere for 4 hr. Removal of the catalyst and the solvent left 3-[3-imidazo-1-15 ylpropyloxy]]- aniline was then coupled with 319A as described for 570 to afford 576 (HPLC retention time (YMC ODS S5 4.6 x 30 mm): 1.33 min). Beginning with 4-nitrophenol and 1-chloro-3-[imidazo-1-yl]-propane 577 (HPLC retention time (YMC ODS S5 4.6 x 30 mm): 1.42 min) was

20 prepared in a similar manner as 576.

## Example 578

# N-(2-Chloro-6-methylphenyl)-2-[[4-[2-(1H-imidazol-1-yl)ethoxy]-3-methoxyphenyl]amino]-5-thiazolecarboxamide

Beginning with 2-methoxy-4-nitrophenol and 1-chloro-3-[imidazo-1-yl]-ethane, **578** (HPLC retention time (YMC ODS S5 4.6 x 30 mm): 1.35 min) was prepared in a similar manner as **576**.

## Example 579

10 N-(2-Chloro-6-methylphenyl)-2-[[3-[[[3-(1H-imidazol-1-yl)propyl]amino]sulfonyl]phenyl]amino]-5-thiazolecarboxamide

and

## Example 580

15 N-(2-Chloro-6-methylphenyl)-2-[[4-[[[3-(1H-imidazol-1-yl)propyl]amino]sulfonyl]phenyl]amino]-5-thiazolecarboxamide

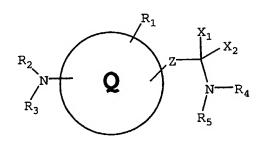
3-Imidazo-1-yl-propylamine (2.04 mL, 2.5 eq) was added to a solution of 3-nitro-benzenesulfonyl chloride (1.5 gm, 6.77 mmole) in THF (20 mL) at

RT. After 1 hr, the solvent was removed and the residue was partitioned between water and a mixture of 10% MeOH in DCM. The organic phase was separated, washed with water and dried (Na2SO4). The crude N-[3-[imidazo-1-yl]-propyl]-3-nitro-benzenesulfonamide was treated with 10% palladium on charcoal (2 gm) in THF (60 mL) under a hydrogen atmosphere overnight. Removal of the catalyst and then the solvent left crude 3-amino-N-[3-[imidazo-1-yl]-propyl]-benzenesulfonamide which was then coupled with 319A as described for 570 to afford 579 (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.22 min). Beginning with 4-nitro-benzenesulfonyl chloride and 3-[imidazo-1-yl]-propylamine, 580 (HPLC retention time (YMC ODS S7 3 x 50 mm): 1.21 min) was prepared in a similar manner as 579.

15

#### What is claimed is:

1. A cyclic compound of the following formula I or a salt thereof:



5

where

Q is:

10 (1) a 5-membered heteroaryl ring;

(2) a 6-membered heteroaryl ring; or

(3) an aryl ring;

optionally substituted with one or more groups R<sub>i</sub>;

Z is:

15 (1) a single bond;

(2)  $-R_{15}C=CH-$ ; or

(3)  $-(CH_2)_m$ -, where m is 1 to 2;

 $X_1$  and  $X_2$  are each hydrogen, or together form =0 or =S;

20  $R_1$  is:

25

(1) hydrogen or  $R_6$ ,

where  $R_{\epsilon}$  is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or more groups  $Z_3$ ;

(2) -OH or -OR<sub>6</sub>;

```
(3) -SH or -SR_s;
```

- (4)  $-C(O)_{0}H_{1}$ ,  $-C(O)_{0}R_{6}$ , or  $-O-C(O)_{0}R_{6}$ , where q is 1 or 2;
- (5)  $-SO_3H \text{ or } -S(O)_aR_6$ ;
- (6) halo;
- 5 (7) cyano;
  - (8) nitro;
  - (9)  $-Z_4-NR_7R_8$ ;
  - (10)  $-Z_4-N(R_0)-Z_5-NR_{10}R_{11}$ ;
  - (11)  $-Z_4-N(R_{12})-Z_5-R_6;$
- 10 (12)  $-P(O)(OR_6)_2$ ;

 $R_2$  and  $R_3$  are each independently:

- (1) hydrogen or  $R_6$ ;
- (2)  $-Z_4-R_6$ ; or
- (3)  $-Z_{13}-NR_{7}R_{8}$ ;
- 15  $R_4$  and  $R_5$ :
  - (1) are each independently hydrogen or R<sub>6</sub>;
  - (2)  $-Z_4-N(R_9)-Z_5-NR_{10}R_{11}$ ;
  - (3)  $-N(R_9)Z_4R_6$ ; or
- (4) together with the nitrogen atom to which they are attached complete a 3- to 8-membered saturated or unsaturated heterocyclic ring which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ , which heterocyclic ring may optionally have fused to it a benzene ring itself unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ;
- 25  $R_7$ ,  $R_8$ ,  $R_9$ ,  $R_{10}$ ,  $R_{11}$  and  $R_{12}$ :
  - (1) are each independently hydrogen or  $R_s$ ;
- (2) R<sub>7</sub> and R<sub>8</sub> may together be alkylene, alkenylene or
  heteroalkyl, completing a 3- to 8-membered saturated
  or unsaturated ring with the nitrogen atom to which
  they are attached, which ring is unsubstituted or
  substituted with Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>; or

(3) any two of  $R_9$ ,  $R_{10}$  and  $R_{11}$  may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ;  $R_{13}$  is:

```
(1)
                     cyano;
                     nitro;
           (2)
                     -NH,;
           (3)
                     -NHOalkyl;
10
           (4)
                     -OH;
           (5)
                     -NHOaryl;
           (6)
                     -NHCOOalkyl;
           (7)
            (8)
                    -NHCOOaryl;
15
           (9)
                     -NHSO,alkyl;
            (10)
                     -NHSO2aryl;
           (11)
                     aryl;
            (12)
                     heteroaryl;
            (13)
                     -Oalkyl; or
20
                     -Oaryl;
           (14)
      R<sub>14</sub> is:
                     -NO<sub>2</sub>;
           (1)
                     -COOalkyl; or
           (2)
           (3)
                     -COOaryl;
25
      \mathbf{R}_{15} is:
                     hydrogen;
           (1)
           (2)
                     alkyl;
           (3)
                     aryl;
                     arylalkyl; or
           (4)
                     cycloalkyl;
30
           (5)
```

(1) hydrogen or Z<sub>6</sub>, where Z<sub>6</sub> is (i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, aryl, aralkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is substituted by one or more of the following groups (2) to (16) of the definition of Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>;

- (2) -OH or -O $\mathbb{Z}_6$ ;
- 10 (3) -SH or -S $\mathbb{Z}_6$ ;
  - (4)  $-C(O)_{0}H$ ,  $-C(O)_{0}Z_{6}$ , or  $-O-C(O)_{0}Z_{6}$ ;
  - (5)  $-SO_3H$ ,  $-S(O)_0Z_6$ ; or  $S(O)_0N(Z_9)Z_6$ ;
  - (6) halo;
  - (7) cyano;
- 15 (8) nitro;
  - (9)  $^{\prime}$ -Z<sub>4</sub>-NZ<sub>7</sub>Z<sub>8</sub>;
  - (10)  $-Z_4-N(Z_9)-Z_5-NZ_7Z_8;$
  - (11)  $-Z_4-N(Z_{10})-Z_5-Z_6;$
  - (12)  $-Z_4-N(Z_{10})-Z_5-H;$
- 20 (13) oxo;

25

- (14)  $-O-C(O)-Z_6$ ;
- (15) any two of  $Z_1$ ,  $Z_2$ , and  $Z_3$  may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; or
- (16) any two of  $Z_1$ ,  $Z_2$ , and  $Z_3$  may together be -O-( $CH_2$ )<sub>r</sub>-O- ,where r is 1 to 5, completing a 4- to 8-membered ring together with the atoms to which they are attached;

 $Z_4$  and  $Z_5$  are each independently:

- 30 (1) a single bond;
  - (2)  $-Z_{11}-S(O)_{g}-Z_{12}-;$

```
(3) -Z_{11}-C(O)-Z_{12}-;
```

- (4)  $-Z_{11}-C(S)-Z_{12}-;$
- (5)  $-Z_{11}-O-Z_{12}-;$
- (6)  $-Z_{11}-S-Z_{12}-;$

5  $-Z_{11}$ -O-C(O)- $Z_{12}$ -; or

(8)  $-Z_{11}$ -C(O)-O- $Z_{12}$ -;

 $Z_7$ ,  $Z_8$ ,  $Z_9$  and  $Z_{10}$ :

(1) are each independently hydrogen or Z<sub>s</sub>;

(2)  $Z_7$  and  $Z_8$ , or  $Z_6$  and  $Z_{10}$ , may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ; or

(3)  $Z_7$  or  $Z_8$ , together with  $Z_9$ , may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ;

 $\mathbf{Z}_{_{11}}$  and  $\mathbf{Z}_{_{12}}$  are each independently:

- 20 (1) a single bond;
  - (2) alkylene;
  - (3) alkenylene; or
  - (4) alkynylene; and

 $\mathbf{Z}_{13}$  is:

- 25 (1) a single bond;
  - (2)  $-Z_{11}-S(O)_{0}-Z_{12}-;$
  - (3)  $-Z_{11}$ -C(O)- $Z_{12}$ -;
  - (4)  $-Z_{11}$ -C(S)- $Z_{12}$ -;
  - (5)  $-Z_{11}-O-Z_{12}-;$
- 30 (6)  $-Z_{11}-S-Z_{10}-$ ;
  - (7)  $-Z_{11}$ -O-C(O)- $Z_{12}$ -;

- $-Z_{11}-C(O)-O-Z_{12}-;$ 
  - (9)  $-C(NR_{13})$ -;
  - (10)  $-C(CHR_{14})$ -; or
  - (11)  $-C(C(R_{14})_2)$ -.
- 5 providing that said compound is other than
  - (a) a compound of formula (i)

$$\begin{array}{c|c} R_{2a} & & & \\ R_{3a} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ &$$

where

10 R<sub>1a</sub> is alkyl or -C(O)NHNH<sub>2</sub>;

 $R_{\mbox{\tiny 2a}}$  and  $R_{\mbox{\tiny 3a}}$  are independently hydrogen, alkyl, -C(O)-(alk); and

 $R_{4a}$  is hydrogen and  $R_{5a}$  is aryl, alkyl-substituted aryl, halosubstituted aryl, aralkyl, cycloalkyl or amino;

Or  $R_{4a}$  is alkyl and  $R_{5a}$  is alkyl or aryl;

Or  $R_{4a}$  and  $R_{5a}$  together with the nitrogen atom to which they are bonded together from morpholino.

### (b) a compound of formula (ii) or (iii)

where

X is oxygen or sulfur;

R<sub>16</sub> is hydrogen, halogen, alkyl or haloalkyl,

20

 $R_{\mbox{\tiny 2b}}$  is hydrogen, alkyl, aryl, aralkyl, heterocycle, heterocyclealkyl

 $R_{\mbox{\tiny 3b}}$  is alkyl, aryl, aralkyl, heterocycle, heterocyclealkyl

 $R_{4b}$  is hydrogen, alkyl, or aralkyl; and

 $R_{\mbox{\scriptsize 5b}}$  is hydrogen, alkyl, aryl, aralkyl, heterocycle or heterocyclealkyl

### (c) a compound of formula (iv)

···h

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 $R_{\mbox{\tiny 4d}}$  and  $R_{\mbox{\tiny 5d}}$  are independently hydrogen, alkyl, alkenyl, or phenyl;

R<sub>27</sub> is hydrogen or alkyl;

### (d) a compound of formula (v)

$$R_{3e}$$
 $R_{51}$ 
 $R_{52}$ 
 $R_{53}$ 
 $R_{53}$ 
 $R_{52}$ 
 $R_{53}$ 
 $R_{52}$ 
 $R_{54}$ 

where

R<sub>3e</sub> is phenyl, pyridyl or pryimidinyl optionally substituted with halogen or alkyl;

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> $R_{\scriptscriptstyle{50}}$  and  $R_{\scriptscriptstyle{51}}$  are each independently hydrogen, halogen or alkyl;

 $R_{s2}$  and  $R_{s3}$  are each independently hydrogen, halogen, alkyl or haloalkyl;

 $R_{\scriptscriptstyle{56}}$  and  $R_{\scriptscriptstyle{56}}$  are each independently hydrogen, halogen, alkyl, nitro or amino;

 $R_{ss}$  is hydrogen, halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio, or alkoxycarbonyl; and n is zero or 1.

10

5

### (e) a compound of formula (vi)

$$\begin{array}{c|c} R_{2f} & Me \\ \hline \\ R_{3f} & \\ \hline \\ R_{5f} & (vi) \end{array}$$

where

15  $R_{af}$  and  $R_{af}$  are independently hydrogen or alkyl

 $R_{4f}$  is hydrogen or alkyl; and

R<sub>sr</sub> is alkyl, cycloalkyl, aryl, alkyl-substituted aryl, haloalkylsubstituted aryl, halo-substituted aryl, alkoxysubstituted aryl, nitro-substituted aryl, aryl-substituted

aryl, aralkyl, or heteroaryl;

or  $R_{\mbox{\tiny 4f}}$  and  $R_{\mbox{\tiny 5f}}$  together with the nitrogen atom to which they are bonded form a morpholino ring

(f) a compound of formula (vii)

.25

$$\begin{array}{c|c} R_{2g} & N & Me \\ \hline R_{3g} & N & R_{4g} \\ \hline R_{5g} & (Vii) \end{array}$$

where

 $R_{2g}$  is H or -N=O;

 $R_{3g}$  is H or alkyl;

 $R_{_{4g}}$  is H or alkyl; and

 $R_{sg}$  is alkyl, aryl, or aralkyl.

# (g) a compound of formula (viii)

$$R_{1h}$$
 $R_{57}$ 
 $NH$ 
 $R_{57}$ 
 $(viii)$ 

10

5

where

 $R_{1h}$  is alkyl or haloalkyl; and

 $R_{\rm 57}$  is alkyl, alkoxy, alkenyl, akenyloxy, alkynyl, alkynyloxy, cycloalkyl, cycloakenyl, cycloalkoxy, cycloalkenyloxy, or phenyl

15

(h) a compound of formula (ix)

where

R<sub>2</sub> is hydrogen or alkyl;

 $R_{3i}$  is -C(O)-NH-(alk); and

5  $R_{58}$  and  $R_{59}$  are independently hydrogen, alkyl or halogen.

### (i) a compound of formula (x)

10 where

 $R_{5j}$  is alkynyl; and

 $R_{\mbox{\tiny 61}}$  and  $R_{\mbox{\tiny 62}}$  are independently alkoxy or haloalkoxy.

(j) a compound of formula (xi)

$$R_{5k}$$
 $N$ 
 $R_{1k}$ 
 $R_{1k}$ 
 $R_{1k}$ 
 $R_{1k}$ 
 $R_{1k}$ 

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where

 $R_{ik}$  is hydrogen, alkyl, aryl or aralkyl;

\*R<sub>1k</sub> is alkyl, aryl or aralkyl;

 $R_{3k}$  and  $R_{5k}$  are independently alkyl, aryl or aralkyl.

5

# (k) a compound of formula (xii)

$$R_{2m}$$
 $R_{2m}$ 
 $R_{3m}$ 
 $R_{3m}$ 
 $R_{3m}$ 
 $R_{3m}$ 
 $R_{3m}$ 
 $R_{3m}$ 
 $R_{3m}$ 
 $R_{3m}$ 
 $R_{3m}$ 
 $R_{3m}$ 
 $R_{3m}$ 
 $R_{3m}$ 
 $R_{3m}$ 
 $R_{3m}$ 

10

where

 $R_{\mbox{\tiny 2m}}$  is hydrogen or alkyl; and

 $R_{\mbox{\tiny 3m}}$  is the radical of an anthraquinone, phthalocyanine, formazan, nitroaryl, dioxazine, phenazine or stilbene dye stuff.

15

#### (1) a compound of formula (xiii)

$$R_{2n}$$
 $R_{3n}$ 
 $R_{3n}$ 
 $R_{4}$  (xiii)

where

20

 $R_{in}$  is aralkyl or -(alk)C(O)-(aryl);

 $R_{\mbox{\tiny 2n}}$  is hydrogen, alkyl, alkenyl, hydroxyalkyl; and

 $R_{3n}$  is aralkyl

### (m) a compound of formula (xiv)

$$R_1$$
 $R_{1}$ 
 $R_{1}$ 
 $R_{2p}$ 
 $R_{3p}$ 
 $R_{3p}$ 
 $R_{2p}$ 
 $R_{3p}$ 

. 5 where

 $R_{\mbox{\tiny 2p}}$  and  $R_{\mbox{\tiny 3p}}$  are independently hydrogen, alkyl, alkenyl, alkoxy, -CHO, -C(O)-(alk), -COO-(alk), -(alky)-COO-(alk), alkylthioalkyl, or aryl; and

 $R_{\mbox{\tiny 5p}}$  is optionally substituted phenyl.

10

# (n) a compound of formula (xv), (xvi) or (xvii)

$$R_{1}$$
 $R_{1}$ 
 $R_{2q}$ 
 $R_{3q}$ 
 $R_{3q}$ 
 $R_{2r}$ 
 $R_{3r}$ 
 $R_{3r}$ 
 $R_{4r}$ 
 $R_{3r}$ 
 $R_{4r}$ 
 $R_{5r}$ 
 $R_{4r}$ 
 $R_{5r}$ 
 $R_{4r}$ 
 $R_{5r}$ 
 $R_{4r}$ 
 $R_{5r}$ 
 $R_{4r}$ 
 $R_{5r}$ 
 $R_{4r}$ 
 $R_{5r}$ 
 $R_{4r}$ 

15

where

X is oxygen or sulfur;

 $R_{2q}$  is hydrogen

 $R_{3\alpha}$  optionally substituted phenyl;

R<sub>4q</sub> is hydrogen;

 $R_{_{5q}}$  is optionally substituted phenyl;

 $R_{\mbox{\tiny 2r}}$  and  $R_{\mbox{\tiny 3r}}$  are each independently hydrogen, alkyl, or aralkyl;

 $R_{4r}$  is hydrogen; and

 $R_{sr}$  is optionally substituted phenyl;

# (o) a compound of formula (xviii)

10

5

where

X is oxygen or sulfur,

 $R_{2s}$  is hydrogen;

R<sub>3s</sub> is optionally substituted phenyl;

R4 is hydrogen; and

 $R_{5s}$  is optionally substituted phenyl;

### (p) a compound of formula

20

5

# (q) a compound of the formula

$$H_2N$$
 $S$ 
 $SO_2NH_2$ 
 $SO_2NH_2$ 
 $SO_2NH_2$ 

(r) the compound

5 2. A compound of claim 1 wherein said compound is other than a compound of formula (xxi)

$$R_{2aa} = N \qquad N \qquad R_{5aa} \qquad (xxi)$$

where

R<sub>2aa</sub> is hydrogen, or alkyl;

10 R<sub>3aa</sub> is cycloalkyl, aryl, hetercyclo or heteroaryl;

 $R_{\mbox{\tiny 4aa}}$  is aryl or heteroaryl; and

 $R_{\mbox{\tiny baa}}$  is hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, heteroaryl, aralkyl, or heteroaralkyl

3. A compound of claim 1 wherein said compound is other than a compound of formula (xxii)

where

R<sub>lab</sub> is hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, carboxy, alkoxycarbonyl or aralkoxycarbonyl

R<sub>2ab</sub> is hydrogen, alkyl, cycloalkyl, or heteroaryl;

 $R_{\mbox{\tiny 3ab}}$  is hydrogen, alkyl, cycloalkyl, heteroaryl, or

 $-C(O)N(R_{64})-(CH_2)_n-R_{66}$ ; provided  $R_{2b}$  and  $R_{3b}$  are not both hydrogen;

R<sub>4ab</sub> is hydrogen, alkyl or cycloalkyl;

 $R_{5ab}$  is a group of the formula

$$-\frac{1}{2}\left(\operatorname{arylene}\right)_{d}\left(\operatorname{CH}_{2}\right)_{e}\left(\stackrel{B}{\operatorname{N}}\right)_{f}\left(\stackrel{A}{\operatorname{NH}}\right)_{g}\left(\operatorname{CH}_{2}\right)_{h}\left(\stackrel{C}{\operatorname{CH}}\right)_{i}\left(\operatorname{CH}_{2}\right)_{j}\operatorname{COOH}$$

$$\left(\stackrel{C}{\operatorname{CO}}\right)_{k}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left(\stackrel{NH}{\operatorname{NH}}\right)_{1}\left($$

where

A is carbonyl or sulphonyl;

B is hydrogen, alkyl or cycloalkyl;

 $R_{63}$  is aryl, aralkyl, heterocycle, heterocyclealkyl, hydroxy, hydrogen or alkyl;

or R<sub>63</sub> is carboxy, carboxyalkyl, alkyl-O-CO-, aralkyl-O-CO-, alkyl-CO-, aralkyl-CO-, heteralkyl-CO-, alkylsulphonyl, arylsulphonyl or heteroarylsulphonyl and k is zero;

- or  $R_{cs}$  is an alpha-amino acid bonded via the amino group and l is zero and k is 1;
- d, f, g, k, l and m are each independently zero or 1, whereby m is not zero when f or g is 1;

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i is zero or 1 whereby k and l are also zero when i is zero;

e is zero to 3;

h is zero to 5;

j is zero to 2; and

the sum of e, h and j is 2 to 7.

R<sub>64</sub> is hydrogen, alkyl, cycloalkyl, or heteroaryl;

 $R_{\mbox{\tiny 65}}$  is hydrogen, alkyl, cycloalkyl, aryl or heteroaryl;

n is an integer zero to 4.

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4. A compound of claim 1 wherein said compound is other than a compound of formula (xxiii)

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where R<sub>66</sub> is a heterocycle;

5. A compound of claim 1 wherein said compound is other than a compound of formula (xxiv) or (xxv)

**20** 

A compound of claim 1 wherein said compound is other than
 (a) a compound of formula (xxvi)

$$\begin{array}{c|c} & & & & \\ & & & & \\ R_{4ba} & & & \\ R_{5ba} & & & \\ \end{array}$$

where D, E, F, G and J are selected from carbon and nitrogen such to form a six-membered heteroaryl ring known in the chemical arts;

 $R_{\mbox{\tiny 2ba}}$  is hydrogen, alkyl, cycloalkyl, akenyl, alkynyl, aryl, heteroaryl, heterocyclo, sulfonyl, trihalomethanesulfonyl, hydroxy, alkoxy, and carboxy;

Z is oxygen or sulfur;

A is selected from oxygen, nitrogen and sulfur;

B is selected from nitrogen and sulfur;

 $R_{4ba}$  and  $R_{5ba}$  are independently hydrogen, alkyl, cycloalkyl, aryl, carbonyl, carboxy, sulfonyl, trihalomethanesulfonyl,

Or  $R_{4ba}$  and  $R_{5ba}$  together form a five or six-membered heterocyclic ring;

Wherein the heteroaryl ring containing A and B is optionally substituted.

(b) a compound of formula (xxvii)

where

 $R_{2bb}$  is hydrogen or alkyl or haloalkyl  $R_{3bb}$  is optionally substituted phenyl;  $R_{4bb}$  is hydrogen or alkyl; and

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### $R_{\text{5bb}}$ is optionally substituted phenyl or pyridyl

(c) a compound of formula (xxviii)

5

where

 $R_{2bc}$  is hydrogen, alkyl or cycloalkyl;

 $R_{3bc}$  is hydrogen, alkyl, aryl, or aralkyl;

Or  $R_{2bc}$  and  $R_{3bc}$  together form a heterocyclic ring;

 $R_{4bc}$  is hydrogen or alkyl; and

 $R_{\text{5bc}}$  is aryl

10

(d) a compound of formula (xxix)

where

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 $R_{\text{1bd}}$  is alkyl, carboxy, hydroxyalkyl, haloalkyl, alkylthio, hydroxyiminoalkyl or alkenyl;

 $R_{\mbox{\tiny 2bd}}$  and  $R_{\mbox{\tiny 3bd}}$  are independently hydrogen, alkyl, pyridyl, acyl, aryl, aralkyl or guanidino; and

 $R_{\mbox{\tiny 4bd}}$  and  $R_{\mbox{\tiny 5bd}}$  together form an unsaturated heterocyclic ring

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(e) a compound where R<sub>3</sub> is alkyl, alkenyl, alkynyl, cycloalkenylalkyl, or aralkyl when

- (a) Q is pyridine, thiophene, furan, pyrrole, pyrazole, thiazole or isothiazole, and
- (b) R2 is hydrogen or alkyl,

5 (f) a compound of formula (xxx)

$$\begin{array}{c|c}
R_2 & & \\
R_3 & & \\
R_{1be} & & \\
\end{array}$$
(xxx)

where

 $R_{\text{lbe}}$  is aralkyl;

10 (g) a compound where  $R_3$  is a group of the formula

Where Z is nitrogen or carbon; and

R\* and R\*\* are independently hydrogen, halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, araloxy, alkoxyalkyl, cycloalkyl, alkenyl, alkenyloxy, alkynyl, alkynyloxy, alkylthioalkyl, or amino; or

- (h) a compound where either  $R_2$  or  $R_3$  is heteroaryl.
- 7. A compound of claim 1, wherein Z is a bond and  $X_1$  and  $X_2$  together form =0 or =S.
  - 8. A compound of claim 7, wherein R<sub>1</sub> is hydrogen, halo, alkyl, aryl, alkoxy, alkoxycarbonyl, or aryloxycarbonyl.

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- 9. A compound of claim 8, wherein R, is hydrogen.
- 10. A compound of claim 7, wherein R<sub>2</sub> is hydrogen.
- 5 11. A compound of claim 7, wherein  $R_3$  is  $-Z_4-R_6$  or  $-Z_{13}-NR_7R_8$ .
  - 12. A compound of claim 7, wherein  $R_2$  is other than heteroaryl and  $R_3$  is aryl which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or more groups  $Z_3$ .

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- 13. A compound of claim 7, wherein R<sub>4</sub> is hydrogen.
- 14. A compound of claim 7, wherein  $R_s$  is an aryl group which is substituted with  $Z_1$ ,  $Z_2$  and one or more groups  $Z_3$ .

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- 15. A compound of claim 7 wherein Q is thiazole.
- 16. A compound of claim 15, wherein  $R_3$  is  $-Z_4-R_6$  wherein  $Z_4$  is a single bond and  $R_6$  is aryl or heteroaryl which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or more groups  $Z_3$ .
  - 17. A compound of claim 16 wherein  $R_6$  is aryl substituted with at least one group  $Z_3$  where  $Z_3$  is  $-Z_4$ -NZ<sub>7</sub>Z<sub>8</sub> where  $Z_4$  is a bond  $Z_7$  is hydrogen or alkyl and  $Z_8$  is heterocyclo-substituted alkyl.

25

18. A compound of claim 17 wherein  $R_1$  is hydrogen or alkyl,  $R_2$  and  $R_4$  are independently hydrogen or alkyl, and  $R_5$  is aryl which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or more groups  $Z_3$ .

19. A compound of claim 16 wherein  $R_6$  is heteroaryl substituted with at least one group  $Z_3$  where  $Z_3$  is  $-Z_4$ -NZ<sub>7</sub>Z<sub>8</sub> where  $Z_4$  is a bond  $Z_7$  is hydrogen or alkyl and  $Z_8$  is heterocyclo-substituted alkyl.

- 5 20. A compound of claim 16 wherein  $R_{\scriptscriptstyle 6}$  is heteroaryl substituted with at least one group  $Z_{\scriptscriptstyle 3}$  where  $Z_{\scriptscriptstyle 3}$  is alkyl.
- 21. A compound of claim 20 wherein  $R_1$  is hydrogen or alkyl,  $R_2$  and  $R_4$  are independently hydrogen or alkyl, and  $R_5$  is aryl which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or more groups  $Z_3$ .
  - 22. A compound of claim 1, wherein each compound of the formula I or salt thereof is selected from the group consisting of:

[5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-methyl-2-

thiazolyl]carbamic acid, 1,1-dimethylethyl ester;

[5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-trifluoromethyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester;

2-Amino-N-(2,4,6-trimethylphenyl)-4-trifluoromethyl-5-thiazolecarboxamide, trifluoroacetate (1:1);

[5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-phenyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester;

2-Amino-N-(2,4,6-trimethylphenyl)-4-phenyl-5-thiazolecarboxamide, trifluoroacetate (1:1);

[5-{[phenylamino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid,

25 1,1-dimethylethyl ester;

20

[5-[[(2,4-Dichlorophenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester;

5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester;

30 2-Amino-N-(2,4,6-trimethylphenyl)-4-phenyl-5-thiazolecarboxamide, trifluoroacetate (1:1);

[5-[[(2-Methoxy-6-methylphenyl)amino]carbonyl]-4-methyl-2-

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thiazolyl]carbamic acid 1,1-dimethylethyl ester;
            [4-Methyl-5-[[[3-methyl-4-(1-
      methylethyl)phenyl]amino]carbonyl]-2-thiazolyl]carbamic acid 1.1-
  5
      dimethylethyl ester;
              [5-[[(4-Bromo-2,6-dimethylphenyl)amino]carbonyl]-4-methyl-2-
      thiazolyl]carbamic acid 1,1-dimethylethyl ester;
              [4-Methyl-5-[[[2-methyl-6-(1-
      methylethyl)phenyl]amino]carbonyl]-2-thiazolyl]carbamic acid 1,1-
 10
      dimethylethyl ester;
              [5-[[(2,4-Dimethylphenyl)amino]carbonyl]-4-methyl-2-
      thiazolyl]carbamic acid 1,1-dimethylethyl ester;
              [4-Methyl-5-[[(2-methylphenyl)amino]carbonyl]-2-
      thiazolyl]carbamic acid 1,1-dimethylethyl ester;
15
             [5-[[(2-Chloro-6-methylphenyl)amino]carbonyl]-4-methyl-2-
      thiazolyl]carbamic acid 1,1-dimethylethyl ester;
             [5-[[[2-(1,1-Dimethylethyl)-4-methylphenyl]amino]carbonyl]-4-
      methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester;
             [5-[[(2-Furanylmethyl)amino]carbonyl]-4-methyl-2-
     thiazolyl]carbamic acid 1,1-dimethylethyl ester;
20
             [5-[[[3-Methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]-4-
     methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester:
             [5-[[(4-Cyclohexylphenyl)amino]carbonyl]-4-methyl-2-
     thiazolyl]carbamic acid 1,1-dimethylethyl ester;
25
             [5-[[(Cyclohexylmethyl)amino]carbonyl]-4-methyl-2-
     thiazolyl]carbamic acid 1,1-dimethylethyl ester;
             [5-[[(2,3-Dihydro-1H-indenyl)amino]carbonyl]-4-methyl-2-
     thiazolyl]carbamic acid 1,1-dimethylethyl ester;
             [5-[(2,5-Dihydro-1H-pyrrol-1-yl)carbonyl]-4-methyl-2-
30
     thiazolyl]carbamic acid 1,1-dimethylethyl ester;
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[5-[(2,5-Dihydro-2,5-dimethyl-1H-pyrrol-1-yl)carbonyl]-4-
     methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester;
             1-[[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-
     thiazolyl]carbonyl]-L-prolinamide;
 5
             [5-[(4-Formyl-1-piperazinyl)carbonyl]-4-methyl-2-
     thiazolyl]carbamic acid 1,1-dimethylethyl ester;
             [5-(1,4-Dioxa-8-azaspiro[4.5]decan-8-ylcarbonyl)-4-methyl-2-
     thiazolyl]carbamic acid 1,1-dimethylethyl ester;
             [5-[[3-[(Diethylamino)carbonyl]-1-piperidinyl]carbonyl]-4-
10
     methyl-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester;
             [4-Methyl-5-[(octahydro-1-quinolinyl)carbonyl]-2-
     thiazolyllcarbamic acid 1,1-dimethylethyl ester;
             2-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-
     thiazolecarboxylic acid 2-[(1,1-dimethylethoxy)carbonyl]hydrazide;
15
             [5-[[(4-Methoxyphenyl)amino]carbonyl]-4-methyl-2-
     thiazolyl]carbamic acid 1,1-dimethylethyl ester;
             [4-Methyl-5-[[(4-methylphenyl)amino]carbonyl]-2-
     thiazolyl]carbamic acid 1,1-dimethylethyl ester;
             [5-[[(1,2-Dimethylpropyl)amino]carbonyl]-4-methyl-2-
20
     thiazolyl]carbamic acid 1,1-dimethylethyl ester;
             [5-[[(2,2-Dimethylpropyl)amino]carbonyl]-4-methyl-2-
     thiazolyl]carbamic acid 1,1-dimethylethyl ester;
             [4-Methyl-5-[(2-propynylamino)carbonyl]-2-thiazolyl]carbamic
     acid 1,1-dimethylethyl ester;
25
            [4-Methyl-5-[(2-propenylamino)carbonyl]-2-thiazolyl]carbamic
     acid 1,1-dimethylethyl ester;
            [4-Methyl-5-[(methylphenylamino)carbonyl]-2-
     thiazolyl]carbamic acid 1,1-dimethylethyl ester;
            [4-Methyl-5-[[(3,4,5-trimethoxyphenyl)amino]carbonyl]-2-
30
     thiazolyl]carbamic acid 1,1-dimethylethyl ester;
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[5-[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]-4-methyl-2thiazolyl]carbamic acid 1,1-dimethylethyl ester; [5-[[[3-(1H-Imidazol-1-yl)propyl]amino]carbonyl]-4-methyl-2thiazolyl]carbamic acid 1,1-dimethylethyl ester: 5 [5-[[[(3,4-Difluorophenyl)methyl]amino]carbonyl]-4-methyl-2thiazolyl]carbamic acid 1,1-dimethylethyl ester; N-[[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5thiazolyl]carbonyl]-L-leucine methyl ester; 5-[[[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5-10 thiazolyl]carbonyl]amino]-4-oxopentanoic acid methyl ester; [5-[[[2-(Ethylthio) ethyl]amino]carbonyl]-4-methyl-2-thiazolyl] carbamic acid 1,1-dimethylethyl ester; [5-[[Bis(3-methylbutyl)amino]carbonyl]-4-methyl-2thiazolyl]carbamic acid 1,1-dimethylethyl ester; 15 [5-[[Ethyl(1-methylethyl)amino]carbonyl]-4-methyl-2thiazolyl]carbamic acid 1,1-dimethylethyl ester; 2-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-5thiazolecarboxylic acid 2-[[(3,5dichlorophenyl)aminolthioxomethyllhydrazide: 20 [5-[[Bis(2-ethoxyethyl)amino]carbonyl]-4-methyl-2thiazolyl]carbamic acid 1,1-dimethylethyl ester; [4-Methyl-5-[[3-[(trifluoroacetyl)amino]-1pyrrolidinyl]carbonyl]-2-thiazolyl]carbamic acid 1,1-dimethylethyl ester; 25 [5-[[(2,6-Dimethylphenyl)amino]carbonyl]-4-methyl-2thiazolyl]carbamic acid 1,1-dimethylethyl ester; 2-[[(2,2-Dichloro-1-methylcyclopropyl)carbonyl]amino]-4methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide; 2-[(Cyclohexylacetyl)amino]-4-methyl-N-(2,4,6-30 trimethylphenyl)-5-thiazolecarboxamide;

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2-[(2,5-Difluorobenzoyl)amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
             2-[(5-Bromo-2-chlorobenzoyl)amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
 5
             2-[(3-Cyanobenzoyl)amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
             2-[[4-(Acetylamino)benzoyl]amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
             4-Methyl-2-[[3-(trifluoromethyl)benzoyl]amino]-N-(2,4,6-
10
     trimethylphenyl)-5-thiazolecarboxamide;
             4-Methyl-2-[[2-(2-phenylethyl)benzoyl]amino]-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
             2-[(3,5-Dimethylbenzoyl)amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
15
             2-[(4-Ethenylbenzoyl)amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
           2-[(4-Butylbenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-
     5-thiazolecarboxamide:
           4-Methyl-2-[(4-pentylbenzoyl)amino]-N-(2,4,6-trimethylphenyl)-
     5-thiazolecarboxamide;
20
           4-Methyl-2-[(1-oxo-3-phenoxypropyl)amino]-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
           4-Methyl-2-[(1-oxo-3-phenylpropyl)amino]-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
25
           2-[[3-(2-Methoxyphenyl)-1-oxopropyl]amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
           4-Methyl-2-[(2-naphthalenylacetyl)amino]-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
           2-[(Diphenylacetyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-
30
     thiazolecarboxamide:
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2-[[(2-Chloro-6-fluorophenyl)acetyl]amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
            4-Methyl-2-[[(2-methylphenyl)acetyl]amino]-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
 5
           2-[[(3-Methoxyphenyl)acetyl]amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
           2-[[(3,4-Dimethoxyphenyl)acetyl]amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
           2-[[(4-Chlorophenyl)acetyl]amino]-4-methyl-N-(2,4,6-
10
     trimethylphenyl)-5-thiazolecarboxamide;
           2-[([1,1'-Biphenyl]-4-ylacetyl)amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
           4-Methyl-2-[(1-oxo-4-phenylbutyl)amino]-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
15
           2-[(2-Hydroxy-2-phenyl-1-oxopropyl)amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
           2-[(2-Hydroxy-1-oxohexyl)amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
           4-Methyl-2-[[1-oxo-4-(2-thienyl)butyl]amino]-N-(2,4,6-
20
     trimethylphenyl)-5-thiazolecarboxamide;
           4-Methyl-2-[(3-thienylcarbonyl)amino]-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
           2-[(2-Benzofuranylcarbonyl)amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
25
           N-[4-Methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-
     thiazolyl]-4-pyridinecarboxamide, N-oxide;
           6-Chloro-N-[4-methyl-5-[[(2,4,6-
     trimethylphenyl)amino|carbonyl]-2-thiazolyl|-3-pyridinecarboxamide;
           N-[4-Methyl-5-[[(2,4,6-trimethylphenyl)amino] carbonyl]-2-\\
30
     thiazolyl]-3-pyridinecarboxamide;
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N-[4-Methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-
     thiazolyl]-3-quinolinecarboxamide;
            4-Methyl-2-[[(4-nitrophenyl)acetyl]amino]-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
            4-Methyl-2-[(2,4,6-trichlorobenzoyl)amino]-N-(2,4,6-
 5
     trimethylphenyl)-5-thiazolecarboxamide;
            4-Methyl-2-[[2-[[3-(trifluoromethyl)phenyl]amino]benzoyl]
     amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
            4-Methyl-2-[[4-(4-nitrophenyl)-1-oxobutyl]amino]-N-(2,4,6-
10
     trimethylphenyl)-5-thiazolecarboxamide;
            4-Methyl-2-[[4-(methylsulfonyl)benzoyl]amino]-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
            2-[(4-Heptylbenzoyl)amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
            2-[[(2,4-Difluorophenyl)acetyl]amino]-4-methyl-N-(2,4,6-
15
     trimethylphenyl)-5-thiazolecarboxamide;
            (S)-2-[[2-(Dipropylamino)-1-oxopropyl]amino]-4-methyl-N-
     (2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
            2-[(2-Biphenylenecarbonyl)amino]-4-methyl-N-(2,4,6-
20
     trimethylphenyl)-5-thiazolecarboxamide;
           2-[[3-(3-Methoxyphenyl)-1-oxopropyl]amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
           4-Methyl-N-(2,4,6-trimethylphenyl)-2-[[(2,4,6-
     trimethylphenyl)acetyl]amino]-5-thiazolecarboxamide;
           4-Methyl-2-[(1-oxo-6-heptenyl)amino]-N-(2,4,6-trimethylphenyl)-
25
     5-thiazolecarboxamide:
           2-[[(1,3-Benzodioxol-5-yl)acetyl]amino]-4-methyl-N-(2,4,6-
     trimethylphenyl)-5-thiazolecarboxamide;
           4-Methyl-2-[[[2-(phenylmethoxy)phenyl]acetyl]amino]-N-(2,4,6-
```

trimethylphenyl)-5-thiazolecarboxamide;

 $\label{lem:continuous} 4-Methyl-2-[[(3-phenoxyphenyl)acetyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;$ 

- $2\hbox{-}[(3,5\hbox{-}Dimethoxyphenyl)acetyl] amino]-4\hbox{-}methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;}$
- 5 2-[[4-[4-[Bis(2-chloroethyl)amino]phenyl]-1-oxobutyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 4-[[4-[[[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]amino]carbonyl]phenyl]amino]-4-oxobutanoic acid methyl ester;
- 4-Methyl-2-[[(phenylsulfonyl)acetyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[2-(Acetylamino)-1-oxohexyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[4-[(Dipropylamino)sulfonyl]benzoyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
    - 2-[(4-Cyclohexylbenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

15

- 2-[(4-Bromo-3-methylbenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[(2,3-Difluorophenyl)acetyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 4-Methyl-2-[[[4-(1-methylethyl)phenyl]acetyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[[4-(1,1-Dimethylethyl)cyclohexyl]carbonyl]amino]-4-methyl-25 N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - N,N-Dimethyl-N'-[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]butanediamide;
  - 2-[(1,6-Dioxohexyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

2-[(Benzo[b]thiophen-2-ylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

- 2-[(1-Adamantylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 5 4-Methyl-2-[[(4-methylcyclohexyl)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[(1,7-Dioxooctyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[2-(Acetylamino)-4-(ethylthio)-1-oxobutyl]amino]-4-methyl-N10 (2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 1,5-Dimethyl-N-[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-1H-pyrazole-3-carboxamide:
- 2-[[[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2thiazolyl]amino]carbonyl]benzoic acid;
  - N-[4-Methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-6-benzothiazolecarboxamide;
  - 1-Ethyl-4-methyl-N-[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-1H-pyrazole-3-carboxamide;
  - 4-Methyl-2-[[3-[(3H-1,2,3-triazolo[4,5-b]pyridin-3-yloxy)methyl]benzoyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[(2-Furanylcarbonyl)amino]-4-methyl-N-(2,4,6-25 trimethylphenyl)-5-thiazolecarboxamide;

- 2-[(4-Chlorobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- [4-Methyl-5[[(2-nitrophenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester;

[4-Methyl-5[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, phenylmethyl ester;

Methyl[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester;

- 5 [4-Methyl-5-[[methyl(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester;
  - [4-Methyl-5[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]carbamic acid, methyl ester;
- [4-Ethyl-5[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-10 thiazolyl]carbamic acid, 1,1-dimethylethyl ester;
  - [5-[[(2,6-Dichlorophenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, 1,1-dimethylethyl ester;
  - 2-Amino-N-(2-methyl-6-isopropylphenyl)-4-methyl-5-thiazolecarboxamide, trifluoroacetate (1:1);
- 2-(Benzoylamino)-4-methyl-N-(2,4,6-trimethylphenyl)-5thiazolecarboxamide;
  - 4-Methyl-2-[(phenylcetyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[(Acetylamino)acetyl]amino]-4-methyl-N-(2,4,6-20 trimethylphenyl)-6-thiazolecarboxamide;
  - 2-Amino-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarbothioamide;
  - 2-[(4-Bromobenzoyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 4-Methyl-2-[(4-nitrobenzoyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - $2\hbox{-}[(4\hbox{-}Cyanobenzoyl)amino]\hbox{-} 4\hbox{-}methyl\hbox{-}N\hbox{-}(2,4,6\hbox{-}$   $trimethylphenyl)\hbox{-} 5\hbox{-}thiazolecarboxamide};$

4-Methyl-2-[[(5-nitro-2-furanyl)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

4-Methyl-2-[(2-thienylcarbonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

- 4-[[[4-Methyl-5-[[(2,4,6-trimethylphenyl) amino]carbonyl]-2-thiazolyl]amino]carbonyl]benzoic acid methyl ester;
  - 2-[(5-Isoxazolylcarbonyl)amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[(3-Furanylcarbonyl)amino]-4-methyl-N-(2,4,6-
- 10 trimethylphenyl)-5-thiazolecarboxamide;

5

- 2-[[(2,4-Dimethyl-5-thiazolyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[(4-Methoxy-3-thienyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 4-Methyl-2-[[(5-nitro-3-thienyl)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[4-[(4-Chlorophenyl)thio]-3-thienyl]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[(5-Chloro-4-methoxy-3-thienyl)carbonyl]amino]-4-methyl-20 N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[2-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-3-thienyl]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[(2-Acetyl-3-thienyl)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
    - 4-Methyl-2-[[(methylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

 $\label{lem:condition} 4-Methyl-2-[[(4-methylphenyl)amino]carbonyl]amino]-N- \\ (2,4,6-trimethylphenyl)-5-thiazolecarboxamide;$ 

- 4-Methyl-2-[[[(phenylmethyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 5 2-[[(Butylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 4-Methyl-2-[[(propylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[(Cyclohexylamino)carbonyl]amino]-4-methyl-N-(2,4,6trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[(2-Chlorophenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[(3-Fluorophenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[(2,6-Dimethylphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
    - [5-[[(2,4,6-Trimethylphenyl)amino]carbonyl]-4-methyl-2-thiazolyl]carbamic acid, phenyl ester;

15

- 4-Methyl-2-[[[(2-phenylethyl)amino]carbonyl]amino]-N-(2,4,6-20 trimethylphenyl)-5-thiazolecarboxamide
  - $2\hbox{-}[[(Hexylamino) carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;$
  - $2-[[[(1,1-Dimethylethyl)amino]carbonyl]amino]-4-methyl-N-\\ (2,4,6-trimethylphenyl)-5-thiazolecarboxamide;$
  - 2-[[[(3-Fluoro-4-methylphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
    - $2\hbox{-}[[(4\hbox{-}Methoxyphenyl)amino]carbonyl]amino]-4\hbox{-}methyl-N-}\\ (2,4,6\hbox{-}trimethylphenyl)-5\hbox{-}thiazolecarboxamide};$
- 2-[[(Diethylamino)carbonyl]amino]-4-methyl-N-(2,4,6-30 trimethylphenyl)-5-thiazolecarboxamide;

 $2-[[[Bis(1-methylethyl)amino]carbonyl]amino]-4-methyl-N-\\ (2,4,6-trimethylphenyl)-5-thiazolecarboxamide;$ 

- 4-Methyl-2-[[[methyl(phenylmethyl)amino] carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 4-Methyl-2-[[(methylphenylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[(Cyclohexylmethylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 4-Methyl-2-[[(1-phenylethyl)amino]carbonyl]amino]-N-(2,4,6-10 trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[(Cyclopropylmethyl)propylamino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 4-Methyl-2-[[[(4-methylcyclohexyl)amino]carbonyl] amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[(Cyclohexylmethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[(2,3-Dihydro-1H-inden-1-yl)amino]carbonyl]amino]-4-20 methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 4-Methyl-2-[[[(1-naphthalenylmethyl)amino] carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide
  - $2\hbox{-}[[Bis(phenylmethyl)amino] carbonyl] amino]-4-methyl-N- \\ (2,4,6-trimethylphenyl)-5-thiazolecarboxamide;$
- 25 2,6-Dimethyl-N-[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-4-morpholinecarboxamide;
  - 2-Ethyl-N-[4-methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]-2-thiazolyl]-1-piperidinecarboxamide;

1-[[[4-Methyl-5-[[(2,4,6-trimethylphenyl) amino]carbonyl]-2thiazolyl]amino]carbonyl]-3-piperidinecarboxylic acid ethyl ester: 3,3-Dimethyl-N-[4-methyl-5-[[(2,4,6trimethylphenyl)amino]carbonyl]-2-thiazolyl]-1-piperidinecarboxamide 5 1-[[[4-Methyl-5-[[(2,4,6-trimethylphenyl)amino] carbonyl]-2thiazolyl]amino]carbonyl]-4-piperidinecarboxylic acid ethyl ester; 4-Methyl-2-[[[(3-methyl-2-pyridinyl)amino|carbonyl]amino|-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide 4-Methyl-2-[[[1-(phenylmethyl)-4-10 piperidinyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5thiazolecarboxamide; Octahydro-N-[4-methyl-5-[[(2,4,6trimethylphenyl)amino]carbonyl]-2-thiazolyl]-1(2H)quinolinecarboxamide; 15 3,4-Dihydro-N-[4-methyl-5-[[(2,4,6trimethylphenyl)amino]carbonyl]-2-thiazolyl]-2(1H)isoquinolinecarboxamide; 2-[[[(1,5-Dimethylhexyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide; 20 4-Methyl-2-[[[(1-methylheptyl)amino]carbonyl]amino]-N-(2,4,6trimethylphenyl)-5-thiazolecarboxamide; 2-[[[(2-Fluorophenyl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide; 2-[[[(2-Methoxyphenyl)methyl]amino]carbonyl]amino]-4-25 methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide; 2-[[[(2-Ethoxyphenyl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide: 2-[[[(3-Methoxyphenyl)methyl]amino]carbonyl]amino]-4-

methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

2-[[[(4-Chlorophenyl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

- 2-[[[(4-Methoxyphenyl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 5 2-[[[(2,2-Diphenylethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide
  - $2\hbox{-}[[(2\hbox{-}Aminoethyl)phenylamino]carbonyl]amino]-4\hbox{-}methyl-N-}\\ (2,4,6\hbox{-}trimethylphenyl)-5\hbox{-}thiazolecarboxamide;}$
- 2-[[[2-(3-Methoxyphenyl)ethyl]amino]carbonyl] amino]-4-10 methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[[2-(3,4-Dimethoxyphenyl)ethyl]amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[2-(4-Methoxyphenyl)ethyl]amino]carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 4-Methyl-2-[[[(3-phenylpropyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[2-(Cyclohex-1-en-1-yl)ethyl]amino]carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[4-(1,1-Dimethylethyl)cyclohexyl]amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

- 2-[[[(3-Butoxypropyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[[2-(2-Methoxyphenyl)ethyl]amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[[(2-Chloro-4-fluorophenyl)methyl]amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - $2\hbox{-}[[(Hexylmethylamino) carbonyl] amino]-4\hbox{-}methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;}$
- 2-[[[1-(4-Chlorophenyl)ethyl]amino]carbonyl]amino]-4-methyl-30 N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

2-[[[[2-(3-Chlorophenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

- 4-Methyl-2-[[[2-(2-thienyl)ethyl]amino] carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 5 2-[[[[2-(2-Fluorophenyl)ethyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 4-Methyl-2-[[[2-(2-pyridinyloxy)ethyl]amino] carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
    - 2-[[[[(2-Bromo-4,5-dimethoxyphenyl)methyl]
- methylamino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - (E)-2-[[[(3,7-Dimethyl-2,6-octadienyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
    - 2-[[[(2,3-Dihydro-1,4-benzodioxin-2-
- yl)methyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[3-Methoxy-5-
  - (trifluoromethyl)phenyl]amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 20 2-[[[(4-Cyclohexylphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 4-Methyl-2-[[[(5,6,7,8-tetrahydro-1-naphthalenyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 25 2-[[(1-Anthracenylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[(4-Chloro-1-naphthalenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 4-Methyl-2-[[(2-naphthalenylamino)carbonyl]amino]-N-(2,4,6-30 trimethylphenyl)-5-thiazolecarboxamide;

2-[[(1H-Indol-5-ylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

- $2\hbox{-}[[(1,3\hbox{-Benzodioxol-5-ylamino}) carbonyl] amino]-4\hbox{-}methyl-N-\\ (2,4,6\hbox{-}trimethylphenyl)-5\hbox{-}thiazolecarboxamide}$
- 5 4-Methyl-2-[[(2-pyrazinylamino)carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[(5-Chloro-2-pyridinyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 4-Methyl-2-[[[(6-methyl-2-pyridinyl)amino]carbonyl] amino]-N10 (2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 4-Methyl-2-[[[(2-methyl-4-quinolinyl)amino]carbonyl] amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[(2,3-Dihydro-1,4-benzodioxin-6-yl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[([1,1'-Biphenyl]-2-ylamino)carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[(4-Methoxy-2-methylphenyl)amino]carbonyl] amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide
    - $\hbox{4-Methyl-N-(2,4,6-trimethylphenyl)-2-[[[(2,4,6-trimethylphenyl)-2-[[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(2,4,6-trimethylphenyl)-2-[(4,4,6-trimethylphenyl)-2-[(4,4,6-trimethylphenyl)-2-[(4,4,6-trimethylphenyl)-2-[(4,4,6-trimethylphenyl)-2-[(4,4,6-trimethylphenyl)-2-[(4,4,6-trimethylphenyl)-2-[(4,4,6-trimethylphenyl)-2-[(4,4,6-trimethylphenyl)-2-[(4,4,6-trimethylphenyl)-2-[(4,$
- 20 trimethylphenyl)amino|carbonyl|amino|-5-thiazolecarboxamide;
  - 2-[[[2-(2-Hydroxyethyl)phenyl]amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - $2-[[[(3-Methoxyphenyl)amino]carbonyl]amino]-4-methyl-N-\\ (2,4,6-trimethylphenyl)-5-thiazolecarboxamide;$
- 25 2-[[[(4-Methoxy[1,1'-biphenyl]-3-yl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[(3-Acetylphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[[(4-Cyanophenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-30 trimethylphenyl)-5-thiazolecarboxamide;

2-[[[[4-Fluoro-2-(trifluoromethyl)phenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide

- 2-[[(4-Hexyloxyphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 4-[[[4-Methyl-5-[[(2,4,6-trimethylphenyl)amino] carbonyl]-2-thiazolyl]amino]carbonyl]amino]benzoic acid ethyl ester;
  - 2-[[(4-Decylphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 4-Methyl-2-[[(4-propylphenyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide
  - 4-Methyl-2-[[[(3,4,5-trimethoxyphenyl)amino] carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
    - 4-Methyl-2-[[[4-[[(5-methyl-3-

- isoxazolyl)amino]sulfonyl]phenyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 4-[[[4-Methyl-5-[[(2,4,6-trimethylphenyl) amino]carbonyl]-2-thiazolyl]amino]carbonyl]amino]benzoic acid butyl ester;
- 2-[[(1-Isoquinolinylamino)carbonyl]amino]-4-methyl-N-(2,4,6-20 trimethylphenyl)-5-thiazolecarboxamide;
  - 4-Methyl-2-[[[[2-[(phenylmethyl)thio]phenyl] amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 4-Methyl-2-[[[[4-[(5-phenoxypentyl)oxy]phenyl] 25 amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[5-(1,1-Dimethylpropyl)-2-methoxyphenyl] amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

2-[[(1,2-Dihydro-5-acenaphthylenyl)amino] carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

- 4-Methyl-2-[[[(3-phenoxyphenyl) amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide
- 4-Methyl-2-[[[[2-(4-morpholinyl)phenyl]amino] carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - $\label{lem:conditional} 4-Methyl-2-[[[2-(1-piperidinyl)phenyl] amino] carbonyl] amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;$ 
    - 2-[[[(1-Acetyl-2,3-dihydro-1H-indol-6-
- 10 yl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[(2-Bromo-5-methoxyphenyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[[(2,3-Dimethyl-1H-indol-5-yl)amino]carbonyl]amino]-4-15 methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 4-Methyl-2-[[[2-[[(1-

- methylethyl)amino]carbonyl]phenyl]amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[[(3-Bromo-2-methylphenyl)amino]carbonyl]amino]-4-20 methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 2-[[[(4-Methoxybutyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide
  - 2-[[[(3,3-Dimethylbutyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 4-Methyl-2-[[(2-methylbutyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 4-Methyl-2-[[[(3-methylbutyl)amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 2-[[[(2-Methoxyethyl)amino]carbonyl]amino]-4-methyl-N-(2,4,6-30 trimethylphenyl)-5-thiazolecarboxamide;

 $2\hbox{-}[[[2\hbox{-}(Dimethylamino)ethyl]amino]carbonyl]amino]-4\hbox{-}methyl-N-(2,4,6\hbox{-}trimethylphenyl)-5\hbox{-}thiazolecarboxamide};$ 

- 4-Methyl-2-[[[2-(methylthio)ethyl] amino]carbonyl]amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 5 2-[[(Butylamino)carbonyl]amino]-N-(2,3-dihydro-1H-inden-5-yl)-4-methyl-5-thiazolecarboxamide;
  - 2-[[(Butylamino)carbonyl]amino]-N-2-naphthalenyl-4-methyl-5-thiazolecarboxamide;
    - 2-[[(Butylamino)carbonyl]amino]-N-(3-hydroxy-2-
- 10 naphthalenyl)-4-methyl-5-thiazolecarboxamide;
  - 2-[[(Butylamino)carbonyl]amino]-N-(2-fluoro-5-methylphenyl)-4-methyl-5-thiazolecarboxamide;
  - 2-[[(Butylamino)carbonyl]amino]-N-(2,6-dimethylphenyl)-4-methyl-5-thiazolecarboxamide;
- N-(3-Bromo-2,4,6-trimethylphenyl)-2-
  - [[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide;
  - $2\hbox{-}[[(Butylamino)carbonyl]amino]-N\hbox{-}[2,6\hbox{-}dimethyl\hbox{-}3\hbox{-}(1-methylethyl)phenyl]-4-methyl-5-thiazolecarboxamide}$ 
    - N-(2-Bromo-4,6-dimethylphenyl)-2-
- 20 [[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide;
  - 3-[[[2-[[(Butylamino)carbonyl]amino]-4-methyl-5-thiazolyl]carbonyl]amino]-4-methyl-2-thiophenecarboxylic acid methyl ester;
- 2-[[(Butylamino)carbonyl]amino]-4-methyl-N-(2-methyl-6quinolinyl)-5-thiazolecarboxamide;
  - 2-[[(Butylamino)carbonyl]amino]-N-(2,6-dimethoxyphenyl)-4-methyl-5-thiazolecarboxamide;
  - 2-[[(Butylamino)carbonyl]amino]-N-(4-methoxy-2-naphthalenyl)-4-methyl-5-thiazolecarboxamide;

2-[[(Butylamino)carbonyl]amino]-N-(2-methyl-1-naphthalenyl)-4-methyl-5-thiazolecarboxamide;

- 2-[[(Butylamino)carbonyl]amino]-N-[4-(dimethylamino)-2,3,5,6-tetramethylphenyl]-4-methyl-5-thiazolecarboxamide;
- 5 2-[[(Butylamino)carbonyl]amino]-N-(6-methyl-5-quinolinyl)-4-methyl-5-thiazolecarboxamide;
  - 2-[[(Butylamino)carbonyl]amino]-N-[2-(2-hydroxyethyl)-6-methylphenyl]-4-methyl-5-thiazolecarboxamide;
    - 2-[[(Butylamino)carbonyl]amino]-N-(2,6-dimethyl-3-
- 10 nitrophenyl)-4-methyl-5-thiazolecarboxamide;
  - N-(2-Bromo-3,4,6-trimethylphenyl)-2-
  - [[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide;
  - N-(2-Acetyl-6-hydroxyphenyl)-2-[[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide;
- 15 [4-[[[2-[[(Butylamino)carbonyl]amino]-4-methyl-5-thiazolyl]carbonyl]amino]-2,3,5,6-tetramethylphenyl]carbamic acid 1,1-dimethylethyl ester;
  - 2-[[(Butylamino)carbonyl]amino]-N-(2,6-dichlorophenyl)-4-methyl-5-thiazolecarboxamide;
- N-(4-Amino-2,3,5,6-tetramethylphenyl)-2-
  - $\hbox{[[(butylamino) carbonyl]amino]-4-methyl-5-thiazole carbox amide;}\\$ 
    - N-[5-(Acetylamino)-2,4-dimethylphenyl]-2-
  - $\hbox{\hbox{$[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide;}}\\$ 
    - N-(4-Bromo-2,6-dimethylphenyl)-2-
- 25 [[(butylamino)carbonyl]amino]-4-methyl-5-thiazolecarboxamide
  - 2-[[(Butylamino)carbonyl]amino]-N-(2-chloro-6-methylphenyl)-4-methyl-5-thiazolecarboxamide;
  - 4-Methyl-2-[(methylsulfonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

4-Methyl-2-[[(phenylamino)thiocarbonyl]amino]-N-(2,4,6trimethylphenyl)-5-thiazolecarboxamide: 2-[[(Ethylamino)carbonyl]amino]-4-methyl-N-(2,4,6trimethylphenyl)-5-thiazolecarboxamide; 5 N-(2-Chloro-6-methylphenyl)-2-[(cyclopropylcarbonyl)amino]-5thiazolecarboxamide: 2-[[[(1,1-Dimethylethyl)amino]carbonyl]amino]-N-(2-chloro-6methylphenyl)-5-thiazolecarboxamide; 2-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-methyl-N-(2,4,6-10 trimethylphenyl)-5-thiazoleacetamide: 2-Amino-4-methyl-N-(2,4,6-trimethylphenyl)-5thiazoleacetamide: N-(2-Chloro-6-methylphenyl)-2-[(4,6-dimethyl-2pyridinyl)amino]-5-thiazolecarboxamide; 15 N-(2-Chloro-6-methylphenyl)-2-[(4-ethyl-2-pyridinyl)amino]-5thiazolecarboxamide; N-(2-Chloro-6-methylphenyl)-2-[(2,6-dimethyl-4pyrimidinyl)amino]-5-thiazolecarboxamide; N-(2-Chloro-6-methylphenyl)-2-(3-pyridazinylamino)-5-20 thiazolecarboxamide: N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2thienylcarbonyl)amino]-5-thiazolecarboxamide; N-(2-Chloro-6-methylphenyl)-2-[(cyclopropylcarbonyl)amino]-4methyl-5-thiazolecarboxamide; 25 N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(2furanylcarbonyl)amino]-5-thiazolecarboxamide; N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(3thienylcarbonyl)amino]-5-thiazolecarboxamide; N-(2-Chloro-6-methylphenyl)-4-methyl-2-[(3-30 furanylcarbonyl)amino]-5-thiazolecarboxamide:

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trans-N-(2-Chloro-6-methylphenyl)-4-methyl-2-[[(2-
     phenylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-4-methyl-2-[[(2-
     methylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[(cyclobutylcarbonyl)amino]-4-
 5
     methyl-5-thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[(cyclopentylcarbonyl)amino]-4-
     methyl-5-thiazolecarboxamide;
           2-(Benzoylamino)-N-(2-chloro-6-methylphenyl)-4-methyl-5-
10
     thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[(1-oxopropyl)amino]-5-
     thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[(1-oxobutyl)amino]-5-
     thiazolecarboxamide:
           N-(2-Chloro-6-methylphenyl)-2-[(2-ethyl-1-oxobutyl)amino]-5-
15
     thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[[(1-
     phenylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[[(1-
20
     methylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[[(2,2-dichloro-1-
     methylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[[(2-
     methylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide;
25
           N-(2-Chloro-6-methylphenyl)-2-[[(1-
     hydroxycyclopropyl)carbonyl]amino]-5-thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[[(2,2,3,3-
     tetramethylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[[(1-
     cyanocyclopropyl)carbonyl]amino]-5-thiazolecarboxamide;
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N-(2-Chloro-6-methylphenyl)-2-[(cyclobutylcarbonyl)amino]-5-thiazolecarboxamide;

- N-(2-Chloro-6-methylphenyl)-2-{(cyclopentylcarbonyl)amino]-5-thiazolecarboxamide:
- 5 N-(2-Chloro-6-methylphenyl)-2-[(cyclohexylcarbonyl)amino]-5-thiazolecarboxamide:
  - N-(2-Chloro-6-methylphenyl)-2-[(phenylacetyl)amino]-5-thiazolecarboxamide;
- N-(2-Chloro-6-methylphenyl)-2-[(cyclohexylacetyl)amino]-5-10 thiazolecarboxamide;
  - N-(2-Chloro-6-methylphenyl)-2-[(4-pyridinylacetyl)amino]-5-thiazolecarboxamide:
  - N-(2-Chloro-6-methylphenyl)-2-[[(2,5-dimethyl-1H-pyrrol-3-yl)carbonyl]amino]-5-thiazolecarboxamide;
- N-(2-Chloro-6-methylphenyl)-2-[(2-pyridinylcarbonyl)amino]-5-thiazolecarboxamide;
  - N-(2-Chloro-6-methylphenyl)-2-[(3-pyridinylcarbonyl)amino]-5-thiazolecarboxamide;
- N-(2-Chloro-6-methylphenyl)-2-[(4-pyridinylcarbonyl)amino]-5-20 thiazolecarboxamide;
  - N-(2-Chloro-6-methylphenyl)-2-[(3-thienylcarbonyl)amino]-5-thiazolecarboxamide;
  - N-(2-Chloro-6-methylphenyl)-2-[(2-thienylcarbonyl)amino]-5-thiazolecarboxamide:
- N-(2-Chloro-6-methylphenyl)-2-[(2-furanylcarbonyl)amino]-5-thiazolecarboxamide;
  - N-(2-Chloro-6-methylphenyl)-2-[(3-furanylcarbonyl)amino]-5-thiazolecarboxamide:
    - trans-N-(2-Chloro-6-methylphenyl)-2-[[(2-
- 30 phenylcyclopropyl)carbonyl]amino]-5-thiazolecarboxamide;

N-(2-Chloro-6-methylphenyl)-2-[(2-methyl-1-oxopentyl)amino]-5-thiazolecarboxamide;

- 2-(Benzoylamino)-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;
- 2-[(Cyclopropylcarbonyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide;
  - 2-[(Cyclopropylcarbonyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
    - N-(2-Chloro-4,6-dimethylphenyl)-2-

- 10 [(cyclopropylcarbonyl)amino]-5-thiazolecarboxamide;
  - [4-[2-Oxo-2-[(2,4,6-trimethylphenyl)amino]ethyl]-2-
  - thiazolyl]carbamic acid 1,1-dimethylethyl ester;
    - 2-Amino-N-(2,4,6-trimethylphenyl)-4-thiazoleacetamide;
      - 5-Amino-2-methyl-N-(2,4,6-trimethylphenyl)benzamide;
- 2-Amino-5-chloro-N-(2,4,6-trimethylphenyl)- 4-pyrimidinecarboxamide;
  - [4-Methyl-5-[[(2,4,6-trimethylphenyl)amino]carbonyl]- 2-oxazolyl]carbamic acid 1,1-dimethylethyl ester;
    - 2-Amino-4-(methyl)-N-(2,4,6-trimethylphenyl)-5-
- 20 oxazolecarboxamide, trifluoroacetate (1:1);
  - 2-Amino-N-(2,4,6-trimethylphenyl)-5-pyridinecarboxamide;
  - 3-Amino-N-(2,4,6-trimethylphenyl)-4-pyridinecarboxamide;
  - N-(2-Chloro-6-methylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide;
- 25 2-[(6-Amino-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;
  - N-(2-Chloro-6-methylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-thiazolecarboxamide;
- N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-4-pyrimidinyl)amino]-5-30 thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-(2-pyridinylamino)-5-thiazolecarboxamide:

- 'N-(2-Chloro-6-methylphenyl)-2-[(6-methyl-2-pyridinyl)amino]-5thiazolecarboxamide:
  - 'N-(2-Chloro-6-methylphenyl)-2-[(5-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide:
  - 'N-(2-Chloro-6-methylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide:
- 10 'N-(2-Chloro-6-methylphenyl)-2-[(3-methyl-2-pyridinyl)amino]-5-thiazolecarboxamide;
  - '2-[(5-Bromo-3-methyl-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;
- '2-[(6-Amino-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5thiazolecarboxamide;
  - '2-[(5-Bromo-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;
  - 'N-(2-Chloro-6-methylphenyl)-2-[[3-(phenylmethoxy)-2-pyridinyl]amino]-5-thiazolecarboxamide;
- 20 'N-(2-Chloro-6-methylphenyl)-2-[(5-chloro-2-pyridinyl)amino]-5-thiazolecarboxamide:
  - 'N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-2-pyridinyl)amino]-5-thiazolecarboxamide:
- 'N-(2-Chloro-6-methylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-25 thiazolecarboxamide;
  - '2-[(3-Bromo-5-methyl-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;
  - '2-[(2-Amino-3-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;
- 30 '2-[(3-Amino-2-pyridinyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-(4-pyridinylamino)-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-(3-pyridinylamino)-5-thiazolecarboxamide;

- 5 'N-(2-Chloro-6-methylphenyl)-2-[(6-chloro-3-pyridinyl)amino]-5-thiazolecarboxamide;
  - 'N-(2-Chloro-6-methylphenyl)-2-[(2-chloro-3-pyridinyl)amino]-5-thiazolecarboxamide;
- 'N-(2-Chloro-6-methylphenyl)-2-[(6-methoxy-3-pyridinyl)amino]10 5-thiazolecarboxamide;
  - 'N-(2-Chloro-6-methylphenyl)-2-[(3,5-dimethyl-2-pyrazinyl)amino]-5-thiazolecarboxamide;
  - 'N-(2-Chloro-6-methylphenyl)-2-(phenylamino)-5-thiazolecarboxamide;
- 15 'N-(2-Chloro-6-methylphenyl)-2-[(3-ethylphenyl)amino]-5-thiazolecarboxamide;
  - 'N-(2-Chloro-6-methylphenyl)-2-[(3,5-dimethylphenyl)amino]-5-thiazolecarboxamide;
    - 'N-(2-Chloro-6-methylphenyl)-2-[(4,6-dimethyl-2-
- $20 \quad \hbox{pyrimidinyl)} a mino]-5-thia zole carbox a mide; \\$ 
  - 'N-(2-Chloro-6-methylphenyl)-2-[(6-ethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide:
  - 'N-(2-Chloro-6-methylphenyl)-2-[(6-chloro-2-pyrazinyl)amino]-5-thiazolecarboxamide:
- 25 '2-[(3-Aminophenyl)amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;
  - 'N-(2-Chloro-6-methylphenyl)-2-[(3-hydroxyphenyl)amino]-5-thiazolecarboxamide;
- '2-[(3-Bromophenyl)amino]-N-(2-chloro-6-methylphenyl)-5-30 thiazolecarboxamide;

'N-(2,6-Dimethylphenyl)-2-(phenylamino)-5thiazolecarboxamide; 'N-(2,6-Dimethylphenyl)-2-(methylphenylamino)-5thiazolecarboxamide: 5 'N-(2,6-Dimethylphenyl)-2-(2-pyridinylamino)-5thiazolecarboxamide; 'N-(2,6-Dimethylphenyl)-2-[(6-methyl-2-pyridinyl)amino]-5thiazolecarboxamide; 'N-(2,6-Dimethylphenyl)-2-[(4-methyl-2-pyridinyl)amino]-5-10 thiazolecarboxamide; 'N-(2,6-Dimethylphenyl)-2-[(4-ethyl-2-pyridinyl)amino]-5thiazolecarboxamide; 'N-(2,6-Dimethylphenyl)-2-[(4,6-dimethyl-2-pyridinyl)amino]-5thiazolecarboxamide; 15 '2-[(6-Amino-2-pyridinyl)amino]-N-(2,6-dimethylphenyl)-5thiazolecarboxamide: 'N-(2,6-Dimethylphenyl)-2-[(6-ethyl-2-pyridinyl)amino]-5thiazolecarboxamide; 'N-(2,6-Dimethylphenyl)-2-[(6-propyl-2-pyridinyl)amino]-5-20 thiazolecarboxamide: '2-[(2-Amino-3-pyridinyl)amino]-N-(2,6-dimethylphenyl)-5thiazolecarboxamide; '2-[(3-Amino-2-pyridinyl)amino]-N-(2,6-dimethylphenyl)-5thiazolecarboxamide; '2-[(6-Amino-2-methyl-4-pyrimidinyl)amino]-N-(2,6-

- 25 dimethylphenyl)-5-thiazolecarboxamide;
  - 'N-(2,6-Dimethylphenyl)-2-[[6-(4-morpholinyl)-3pyridazinyl]amino]-5-thiazolecarboxamide;
- '2-[(6-Chloro-3-pyridazinyl)amino]-N-(2,6-dimethylphenyl)-5-30 thiazolecarboxamide;

'N-(2,6-Dimethylphenyl)-2-(3-pyridazinylamino)-5-thiazolecarboxamide;

- '2-[(3-Aminophenyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide;
- 5 '2-[(3-Bromophenyl)amino]-N-(2,6-dimethylphenyl)-5-thiazolecarboxamide;
  - '2-(2-Pyridinylamino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- '2-[(6-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-10 thiazolecarboxamide:
  - '2-[(5-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide:
  - '2-[(4-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- '2-[(3-Methyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide:
  - '2-[(5-Bromo-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - '2-[(5-Chloro-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
    - '2-[(6-Methoxy-3-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
    - '2-[(4-Ethyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
- 25 '2-[(6-Ethyl-2-pyridinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - '2-{(6-Chloro-3-pyridinyl)amino}-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
    - '2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-(2,4,6-
- 30 trimethylphenyl)-5-thiazolecarboxamide;

'2-[(4-Methyl-2-pyrimidinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;

- '2-(2-Pyrazinylamino)-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide
- 5 '2-[(6-Chloro-2-pyrazinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide:
  - '2-[(3,5-Dimethyl-2-pyrazinyl)amino]-N-(2,4,6-trimethylphenyl)-5-thiazolecarboxamide;
  - 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(4-
- morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;
  - 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[3-(4-morpholinyl)propyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;
- 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[methyl[3-(methylamino)propyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;
  - 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(tetrahydro-2-oxo-1H-imidazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-
- 20 thiazolecarboxamide:
  - 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[(2-1H-imidazol-4-ylethyl)amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;
  - 'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-(4-morpholinyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide;
- 25 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(2R)-1-ethyl-2-pyrrolidinyl]methyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide:
  - 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[(2S)-1-ethyl-2-pyrrolidinyl]methyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-

 $\label{lem:condition} \begin{tabular}{ll} $$ '2-[[6-[(2S)-2-(Aminocarbonyl)-1-pyrrolidinyl]-2-methyl-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide; \end{tabular}$ 

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'N-(2-Chloro-6-methylphenyl)-2-[[6-[(2-hydroxyethyl)amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(hydroxymethyl)-1-piperidinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'1-[6-[[5-[[(2-Chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-2-methyl-4-pyrimidinyl]-4-piperidinecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[(3S)-3-methyl-1-piperazinyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'2-[[6-[3-(Acetylamino)-1-pyrrolidinyl]-2-methyl-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1-methyl-2-pyrrolidinyl)ethyl]amino]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[(5-methyl-2-pyrazinyl)methyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

triazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[2-methyl-6-[[2-(1H-1,2,3-

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-

25 morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(dimethylamino)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

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'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(tetrahydro-2-oxo-1H-
     imidazol-1-yl)ethyl]amino]-4-pyrimidinyl]amino]-5-
      thiazolecarboxamide:
          'N-(2-Chloro-6-methylphenyl)-2-[[6-[methyl]2-
 5
     (methylamino)ethyl]amino]-4-pyrimidinyl]amino]-5-
     thiazolecarboxamide:
            'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1-methyl-2-
     pyrrolidinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;
            'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1-
10
     pyrrolidinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;
            'N-(2-Chloro-6-methylphenyl)-2-[[6-[[(1-ethyl-2-
     pyrrolidinyl)methyl]amino]-4-pyrimidinyl]amino|-5-
     thiazolecarboxamide:
           'N-(2-Chloro-6-methylphenyl)-2-[[6-[(4-piperidinylmethyl)amino]-
15
     4-pyrimidinyl]amino]-5-thiazolecarboxamide;
           '2-[[6-[[2-(Acetylamino)ethyl]amino]-4-pyrimidinyl]amino]-N-(2-
     chloro-6-methylphenyl)-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(1H-1,2,3-triazol-1-
     yl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;
20
           'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinyl)-4-
     pyrimidinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-
     morpholinyl)ethyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(4-
25
     morpholinyl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-[methyl]3-
     (methylamino)propyl]amino]-2-pyridinyl]amino]-5-
     thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-[(3S)-3-methyl-1-
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piperazinyl]-2-pyridinyl]amino]-5-thiazolecarboxamide;

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'N-(2-Chloro-6-methylphenyl)-2-[[6-[(3-1H-imidazol-1-
    ylpropyl)amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-[(2-hydroxyethyl)amino]-2-
     pyridinyllamino]-5-thiazolecarboxamide;
 5
           'N-(2-Chloro-6-methylphenyl)-2-[[6-[(2-1H-imidazol-1-
    ylethyl)amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinyl)-2-
     pyridinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4-
10
     morpholinyl)ethyl]amino]-2-pyrazinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(4-
    morpholinyl)propyl]amino]-2-pyrazinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinyl)-2-
     pyrazinyl]amino]-5-thiazolecarboxamide;
15
           'N-(2-Chloro-6-methylphenyl)-2-[[6-[(3S)-3-methyl-1-
     piperazinyl]-2-pyrazinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-(3-hydroxy-1-pyrrolidinyl)-2-
     pyrazinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-(1H-imidazol-1-yl)-2-
20
     pyrazinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-(3-hydroxy-1-pyrrolidinyl)-3-
     pryidazinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[6-(1H-imidazol-1-yl)-3-
    pyridazinyl]amino]-5-thiazolecarboxamide;
25
           'N-(2-Chloro-6-methylphenyl)-2-[[3-(methylamino)-2-
    pyrazinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[3-(3-hydroxy-1-pyrrolidinyl)-2-
    pyrazinyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[3-(cyclopropylamino)-2-
30
    pyrazinyl]amino]-5-thiazolecarboxamide;
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'N-(2-Chloro-6-methylphenyl)-2-[[3-(4-morpholinyl)-2pyrazinyllaminol-5-thiazolecarboxamide: 'N-(2-Chloro-6-methylphenyl)-2-[[3-[[2-(4morpholinyl)ethyl]amino]-2-pyrazinyl]amino]-5-thiazolecarboxamide; 5 '2-[[3-[[2-(Acetylamino)ethyl]amino]-2-pyrazinyl]amino]-N-(2chloro-6-methylphenyl)-5-thiazolecarboxamide; 'N-(2-Chloro-6-methylphenyl)-2-(cyclohexylamino)-5thiazolecarboxamide; 'N-(2-Chloro-6-methylphenyl)-2-(methylamino)-5-10 thiazolecarboxamide: 'N-(2-Chloro-6-methylphenyl)-2-(cyclopropylamino)-5thiazolecarboxamide; 'N-(2-Chloro-6-methylphenyl)-2-[(phenylmethyl)amino]-5thiazolecarboxamide; 15 '2-[[2-(Acetylamino)ethyl]amino]-N-(2-chloro-6-methylphenyl)-5thiazolecarboxamide: 'N-(2-Chloro-6-methylphenyl)-2-[[(1R)-1-(hydroxymethyl)-3methylbutyl]amino]-5-thiazolecarboxamide: 'N-(2-Chloro-6-methylphenyl)-2-[[6-(methoxymethyl)-4-20 pyrimidinyl]amino]-5-thiazolecarboxamide: 'N-(2-Chloro-6-methylphenyl)-2-[[6-hydroxymethyl)-4pyrimidinyl]amino]-5-thiazolecarboxamide; 'N-(2-Chloro-6-methylphenyl)-2-[[6-(4-morpholinylmethyl)-4pyrimidinyl]amino]-5-thiazolecarboxamide; 25 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[2-(dimethylamino)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide: 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(4morpholinyl)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5thiazolecarboxamide:

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[3-(4-morpholinyl)propyl]-amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[[3-(2-oxo-1-pyrrolidinyl)propyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[(2-1H-imidazol-4-ylethyl)amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[(3-1H-imidazol-1-ylpropyl)amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(2-pyridinyl)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide:

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[2-(3-pyridinyl)ethyl]amino]methyl]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

'1-[[6-[[5-[[(2-Chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-4-pyrimidinyl]methyl]-4-piperidinecarboxamide;

'2-[[6-[[[2-(Acetylamino)ethyl]amino]methyl]-4-pyrimidinyl]amino]-N-(2-chloro-6-methylphenyl)-5-

20 thiazolecarboxamide;

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'N-(2-Chloro-6-methylphenyl)-2-(2-naphthalenylamino)-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-(2-quinolinylamino)-5-thiazolecarboxamide:

'N-(2-Chloro-6-methylphenyl)-2-(3-isoquinolinylamino)-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-(2-quinoxalinylamino)-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-4-methyl-2-[[2-methyl-6-(4-30 morpholinyl)-4-pyrimidinyl]amino]-5-thiazolecarboxamide;

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'N-(2-Chloro-6-methylphenyl)-4-methyl-2-[[2-methyl-6-[[2-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]amino]-5-thiazolecarboxamide;
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'2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-phenyl-5-

5 thiazolecarboxamide:

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'2-[(2,6-Dimethyl-4-pyrimidinyl)methylamino]-N-(2-methylphenyl)-5-thiazolecarboxamide;

'2-[(2,6-Dimethyl-4-pyrimidinyl)amino]-N-(2-methylphenyl)-5-thiazolecarboxamide:

10 'N-(3,5-Dimethoxyphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide;

'N-[2,6-Bis(1-methylethyl)phenyl]-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide;

 $\verb"N-(2-Chloro-6-methylphenyl)-2-[2,6-dimethyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-4-methyl-$ 

15 pyrimidinyl)methylamino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[(2,6-dimethyl-4-pyrimidinyl)amino]-N-methyl-5-thiazolecarboxamide;

N-, N-(2-Chloro-6-methylphenyl)-(4-methoxybenzyl)-2-[(6-bromo-2-pyridinyl)amino]-5-thiazolecarboxamide;

N-(2-Chloro-6-methylphenyl)-2-[(6-bromo-2-pyridinyl)amino-5-thiazolecarboxamide:

'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-furanylcarbonyl)-1-piperazinyl]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'2-[[6-[[3-(1H-Benzimidazol-1-yl)propyl]amino]-2-

25 pyridinyl]amino]-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[4-(1H-imidazol-1-yl)butyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[5-(1H-imidazol-1-yl)pentyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide;

'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(4-methyl-1piperazinyl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide; 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[4-(1H-imidazol-1yl)phenyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide; 5 'N-(2-Chloro-6-methylphenyl)-2-[[6-[[6-(1H-imidazol-1yl)hexyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide; 'N-(2-Chloro-6-methylphenyl)-2-[[6-[(3-1H-imidazol-1ylpropyl)amino]-2-pyridinyl]amino]-5-thiazolecarboxamide; '2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-10 (4-methoxyphenyl)-5-thiazolecarboxamide; '2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(4-phenoxyphenyl)-5-thiazolecarboxamide: 'N-(4-Chlorophenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2pyridinyl]amino]-5-thiazolecarboxamide; 15 '2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-[1-(phenylmethyl)-1H-indazol-5-yl]-5-thiazolecarboxamide; 'N-(2-Ethylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2pyridinyl]amino]-5-thiazolecarboxamide; 'N-(2,6-Dimethoxyphenyl)-2-[[6-[[3-(1H-imidazol-1-20 yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide; 'N-(2,4-Dimethoxyphenyl)-2-[[6-[[3-(1H-imidazol-1yl)propyl]amino]-2-pyridinyl]amino]-5-thiazolecarboxamide; '2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-Nphenyl-5-thiazolecarboxamide; 25 '2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-N-(2-methylphenyl)-5-thiazolecarboxamide; 'N-(2-Chlorophenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-2pyridinyl]amino]-5-thiazolecarboxamide; 'N-(2,6-Diethylphenyl)-2-[[6-[[3-(1H-imidazol-1-yl)propyl]amino]-

2-pyridinyl]amino]-5-thiazolecarboxamide;

```
'N-(2-Chloro-6-methylphenyl)-2-[[6-[[3-(1H-imidazol-1-
    yl)propyl]amino]-2-pyridinyl]amino]-4-methyl-5-thiazolecarboxamide;
           '2-[[6-[[3-(1H-Imidazol-1-yl)propyl]amino]-2-pyridinyl]amino]-4-
    methyl-N-[1-(phenylmethyl)-1H-indazol-5-yl]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[3-[[3-(1H-imidazol-1-
5
     yl)propyl]amino]phenyl]amino]-5-thiazolecarboxamide;
           'N-(2-Chloro-6-methylphenyl)-2-[[5-[[3-(1H-imidazol-1-
     yl)propyl]amino]-2-nitrophenyl]amino]-5-thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[(3,4,5-trimethoxy-
     phenyl)amino]-5-thiazolecarboxamide;
10
           N-(2-Chloro-6-methyl-phenyl)-2-[(4-methoxy-phenyl)amino]-5-
     thiazolecarboxamide;
           N-(2-Chloro-6-methyl-phenyl)-2-[(3-methoxy-phenyl)amino]-5-
     thiazolecarboxamide;
           N-(2-Chloro-6-methyl-phenyl)-2-[(2-methoxy-phenyl)amino]-5-
15
     thiazolecarboxamide;
           N-(2-Chloro-6-methyl-phenyl)-2-[(3,5-dimethoxyphenyl)amino]-
     5-thiazolecarboxamide;
           N-(2-Chloro-6-methyl-phenyl)-2-[[4-(dimethylamino)-
     phenyl]amino]-5-thiazolecarboxamide;
20
           N-(2-Chloro-6-methylphenyl)-2-[[4-(4-
     morpholinyl)phenyl]amino]-5-thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[[3-(carboxymethyl)-
     phenyl]amino]-5-thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[[3-(3-carboxypropyl)-
25
     phenyl]amino]-5-thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-[[4-
     (carboxymethyl)phenyl]amino]-5-thiazolecarboxamide;
           N-(2-Chloro-6-methylphenyl)-2-{(2-methyl-1H-benzimidazol-5-
     yl)amino]-5-thiazolecarboxamide;
30
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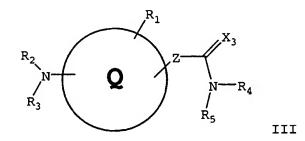
N-(2-Chloro-6-methylphenyl)-2-[[1-[3-(1H-imidazol-1-yl)propyl]-1H-benzimidazol-4-yl]amino]-5-thiazolecarboxamide;

- N-(2-Chloro-6-methylphenyl)-2-[[1-[2-(1H-imidazol-1-yl)ethyl]-1H-indazol-6-yl]amino]-5-thiazolecarboxamide;
- 5 N-(2-Chloro-6-methylphenyl)-2-[[2-[2-(1H-imidazol-1-yl)ethyl]-2H-indazol-6-yl]amino]-5-thiazolecarboxamide;
  - N-(2-Chloro-6-methylphenyl)-2-[(1-methyl-1H-benzimidazol-6-yl)amino]-5-thiazolecarboxamide;
- N-(2-Chloro-6-methylphenyl)-2-[(1-methyl-1H-benzimidazol-5-10 yl)amino]-5-thiazolecarboxamide;
  - N-(2-Chloro-6-methylphenyl)-2-[[2-[3-(1H-imidazol-1-yl)propyl]amino]-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide;
  - N-(2-Chloro-6-methylphenyl)-2-[[2-(4-morpholinylmethyl)-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide;
- N-(2-Chloro-6-methylphenyl)-2-[[2-(1H-imidazol-1-ylmethyl)-1H-benzimidazol-5-yl]amino]-5-thiazolecarboxamide;
  - N-(2-Chloro-6-methylphenyl)-2-[[3-[[5-(1H-imidazol-1-yl)-2-pyridinyl]amino]phenyl]amino]-5-thiazolecarboxamide;
    - N-(2-Chloro-6-methylphenyl)-2-[[3-[3-(1H-imidazol-1-
- 20 yl)propoxy]phenyl]amino]-5-thiazolecarboxamide;

- N-(2-Chloro-6-methylphenyl)-2-[[4-[3-(1H-imidazol-1-yl)propoxy]phenyl]amino]-5-thiazolecarboxamide;
- N-(2-Chloro-6-methylphenyl)-2-[[3-[[[3-(1H-imidazol-1-yl)propyl]amino]sulfonyl]phenyl]amino]-5-thiazolecarboxamide; and
- N-(2-Chloro-6-methylphenyl)-2-[[4-[[[3-(1H-imidazol-1-yl)propyl]amino]sulfonyl]phenyl]amino]-5-thiazolecarboxamide.
- 23 A method for the treatment of a protein tyrosine kinaseassociated disorder, comprising the step of administering to a subject in

need thereof an amount effective therefor of at least one compound of formula III

or a salt thereof:



**5** .

where

Q is:

10 (1) a 5-membered heteroaryl ring;

- (2) a 6-membered heteroaryl ring; or
- (3) an aryl ring;

optionally substituted with one or more groups R<sub>1</sub>;

Z is:

15 (1) a single bond;

(2)  $-R_{15}C=CH-$ ; or

(3)  $-(CH_2)_m$ -, where m is 1 to 2;

 $X_3$  is oxygen or sulfur;

R, is:

20 (1) hydrogen or  $R_6$ ,

where  $R_6$  is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or more groups  $Z_3$ ;

25 more groups Z

- (2) -OH or -O $R_6$ ;
- (3) -SH or -SR<sub>6</sub>;

```
(4) -C(O)_{2}H, -C(O)_{2}R_{8}, or -O-C(O)_{2}R_{6}, where q is 1 or 2;
```

- (5)  $-SO_3H \text{ or } -S(O)_aR_6$ ;
- (6) halo;
- (7) cyano;
- 5 (8) nitro;
  - (9)  $-Z_4-NR_7R_8$ ;
  - (10)  $-Z_4-N(R_9)-Z_5-NR_{10}R_{11}$ ;
  - (11)  $-Z_4-N(R_{12})-Z_5-R_6;$
  - (12)  $-P(O)(OR_6)_2$ ;
- 10  $R_2$  and  $R_3$  are each independently:
  - (1) hydrogen or R<sub>s</sub>;
  - (2)  $-Z_4-R_6$ ; or
  - (3)  $-Z_{13}-NR_{7}R_{8}$ ;

 $R_4$  and  $R_5$ :

- 15 (1) are each independently hydrogen or R<sub>s</sub>;
  - (2)  $-Z_4-N(R_9)-Z_5-NR_{10}R_{11}$ ;
  - (3)  $-N(R_0)Z_4R_6$ ; or
- (4) together with the nitrogen atom to which they are attached complete a 3- to 8-membered saturated or unsaturated heterocyclic ring which is unsubstituted or substituted with Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>, which heterocyclic ring may optionally have fused to it a benzene ring itself unsubstituted or substituted with Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>;

 $R_7$ ,  $R_8$ ,  $R_9$ ,  $R_{10}$ ,  $R_{11}$  and  $R_{12}$ :

30

- 25 (1) are each independently hydrogen or R<sub>s</sub>;
  - (2) R<sub>7</sub> and R<sub>8</sub> may together be alkylene, alkenylene or heteroalkyl, completing a 3- to 8-membered saturated or unsaturated ring with the nitrogen atom to which they are attached, which ring is unsubstituted or substituted with Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>; or

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any two of  $R_9$ ,  $R_{10}$  and  $R_{11}$  may together be alkylene or (3) alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ; 5  $R_{13}$  is: (1) cyano; **(2)** nitro; (3) -NH<sub>2</sub>; 10 -NHOalkyl; **(4) (5)** -OH; -NHOaryl; (6) -NHCOOalkyl; **(7)** -NHCOOaryl; (8) -NHSO2alkyl; 15 (9) (10) -NHSO<sub>2</sub>aryl; (11)aryl; (12)heteroaryl; (13)-Oalkyl; or 20 (14)-Oaryl; R<sub>14</sub> is: -NO<sub>2</sub>; **(1)** -COOalkyl; or **(2)** (3) -COOaryl; 25 R<sub>15</sub> is: **(1)** hydrogen; (2) alkyl;

cycloalkyl;  $Z_1$ ,  $Z_2$  and  $Z_3$  are each independently:

arylalkyl; or

aryl;

(3)

(4)

(5)

(1) hydrogen or  $Z_6$ , where  $Z_6$  is (i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl, cycloalkenyl, cycloalkenyl, cycloalkyl, aryl, aralkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is substituted by one or more of the following groups (2) to (16) of the definition of  $Z_1$ ,  $Z_2$  and  $Z_3$ ;

- (2) -OH or -O $\mathbb{Z}_6$ ;
- 10 (3) -SH or -S $Z_s$ ;
  - (4)  $-C(O)_qH$ ,  $-C(O)_qZ_6$ , or  $-O-C(O)_qZ_6$ ;
  - (5)  $-SO_3H$ ,  $-S(O)_qZ_6$ ; or  $S(O)_qN(Z_9)Z_6$ ;
  - (6) halo;
  - (7) cyano;
- 15 (8) nitro;
  - $(9) -Z_4-NZ_7Z_9;$
  - (10)  $-Z_{1}-N(Z_{9})-Z_{5}-NZ_{7}Z_{8};$
  - (11)  $-Z_4-N(Z_{10})-Z_5-Z_6$ ;
  - (12)  $-Z_4-N(Z_{10})-Z_5-H;$
- 20 (13) oxo;

25

- (14)  $-O-C(O)-Z_6$ ;
- (15) any two of Z<sub>1</sub>, Z<sub>2</sub>, and Z<sub>3</sub> may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; or
- (16) any two of Z<sub>1</sub>, Z<sub>2</sub>, and Z<sub>3</sub> may together be -O-(CH<sub>2</sub>)<sub>r</sub>-O-, where

  r is 1 to 5, completing a 4- to 8-membered ring together

  with the atoms to which they are attached;

 $Z_4$  and  $Z_5$  are each independently:

- 30 (1) a single bond;
  - (2)  $-Z_{11}-S(O)_{0}-Z_{12}-$ ;

```
(3) -Z_{1,1}-C(O)-Z_{1,2}-;
```

- (4)  $-Z_{11}$ -C(S)- $Z_{12}$ -;
- (5)  $-Z_{11}-O-Z_{12}-;$
- (6)  $-Z_{11}-S-Z_{12}-;$
- 5 (7)  $-Z_{11}$ -O-C(O)- $Z_{12}$ -; or
  - (8)  $-Z_{11}$ -C(O)-O- $Z_{12}$ -;

 $Z_7$ ,  $Z_8$ ,  $Z_9$  and  $Z_{10}$ :

- (1) are each independently hydrogen or Z<sub>6</sub>;
- (2)  $Z_7$  and  $Z_8$ , or  $Z_6$  and  $Z_{10}$ , may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ; or
- (3)  $Z_7$  or  $Z_8$ , together with  $Z_9$ , may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ;

 $Z_{11}$  and  $Z_{12}$  are each independently:

- 20 (1) a single bond;
  - (2) alkylene;
  - (3) alkenylene; or
  - (4) alkynylene; and

 $Z_{13}$  is:

- 25 (1) a single bond;
  - (2)  $-Z_{11}-S(O)_{0}-Z_{12}-;$
  - (3)  $-Z_{1,1}-C(O)-Z_{1,2}-;$
  - (4)  $-Z_{11}$ -C(S)- $Z_{12}$ -;
  - (5)  $-Z_{11}$ -O- $Z_{12}$ -;
- 30 (6)  $-Z_{11}-S-Z_{12}-$ ;
  - (7)  $-Z_{11}$ -O-C(O)- $Z_{12}$ -;

- (8)  $-Z_{11}$ -C(O)-O- $Z_{12}$ -;
- (9)  $-C(NR_{13})$ -;
- (10)  $-C(CHR_{14})$ -; or
- (11)  $-C(C(R_{14})_2)-.$
- 5 providing that said compound is other than
  - (a) a compound of formula (i)

$$R_{2a}$$
 $R_{3a}$ 
 $R_{3a}$ 
 $R_{5a}$ 
 $R_{4a}$ 
 $R_{5a}$ 
 $R_{4a}$ 
 $R_{5a}$ 

where

10 R<sub>1a</sub> is alkyl or -C(O)NHNH<sub>2</sub>;

 $R_{\mbox{\tiny 2a}}$  and  $R_{\mbox{\tiny 3a}}$  are independently hydrogen, alkyl, -C(O)-(alk); and

 $R_{4a}$  is hydrogen and  $R_{5a}$  is aryl, alkyl-substituted aryl, halosubstituted aryl, aralkyl, cycloalkyl or amino;

Or  $R_{4a}$  is alkyl and  $R_{5a}$  is alkyl or aryl;

Or  $R_{4a}$  and  $R_{5a}$  together with the nitrogen atom to which they are bonded together from morpholino.

(b) a compound of formula (ii) or (iii)

where

15

20

X is oxygen or sulfur;

 $R_{1b}$  is hydrogen, halogen, alkyl or haloalkyl,

 $R_{2b}$  is hydrogen, alkyl, aryl, aralkyl, heterocycle, heterocyclealkyl

 $R_{3b}$  is alkyl, aryl, aralkyl, heterocycle, heterocyclealkyl

 $R_{\mbox{\tiny 4b}}$  is hydrogen, alkyl, or aralkyl; and

 $R_{\mbox{\tiny 5b}}$  is hydrogen, alkyl, aryl, aralkyl, heterocycle or heterocyclealkyl;

## (c) a compound of formula (vi)

5

10

 $R_{4d}$  and  $R_{5d}$  are independently hydrogen, alkyl, alkenyl, or phenyl;

 $R_{27}$  is hydrogen or alkyl; or.

## 15 (d) the compound

where

24 The method of claim 23, wherein said protein tyrosine kinase-associated disorder is transplant rejection.

20

25 The method of claim 23, wherein said protein tyrosine kinase-associated disorder is rheumatoid arthritis.

26 The method of claim 23, wherein said protein tyrosine kinase-associated disorder is multiple sclerosis.

- 27. The method of claim 23, wherein said protein tyrosine kinaseassociated disorder is inflammatory bowel disease.
  - 28. The method of claim 23, wherein said protein tyrosine kinase-associated disorder is lupus.
- 29. The method of claim 23, wherein said protein tyrosine kinase-associated disorder is graft vs. host disease.
  - 30. The method of claim 23, wherein said protein tyrosine kinase-associated disorder is a T-cell mediated hypersensitivity disease.

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- 31. The method of claim 23, wherein said protein tyrosine kinase-associated disorder is psoriasis.
- 32. The method of claim 23, wherein said protein tyrosine kinaseassociated disorder is Hashimoto's thyroiditis.
  - 33. The method of claim 23, wherein said protein tyrosine kinase-associated disorder is Guillain-Barre syndrome.
- 25 34. The method of claim 23, wherein said protein tyrosine kinase-associated disorder is a cancer.
  - 35. The method of claim 23, wherein said protein tyrosine kinase-associated disorder is contact dermatitis.

36. The method of claim 23, wherein said protein tyrosine kinase-associated disorder is an allergic disease.

- 37. The method of claim 23, wherein said protein tyrosine kinaseassociated disorder is asthma.
  - 38. The method of claim 23, wherein said protein tyrosine kinase-associated disorder is ischemic or reperfusion injury.
- 39. The method of claim 23, wherein said protein tyrosine kinase-associated disorder is atopic dermatitis.
  - 40. The method of claim 23, wherein said protein tyrosine kinase-associated disorder is allergic rhinitis.
  - 41. The method of claim 23, wherein said protein tyrosine kinase-associated disorder is chronic obstructive pulmonary disease.
- 42. The method of claim 23, wherein said protein tyrosine kinase-20 associated disorder is diabetic retinopathy.
  - 43. The method of claim 23, wherein said protein tyrosine kinase is Lck.
- 25 44. The method of claim 23, wherein said protein tyrosine kinase is Fyn.
  - 45. The method of claim 23, wherein said protein tyrosine kinase is Lyn.

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46. The method of claim 23, wherein said protein tyrosine kinase is Hck.

- 47. The method of claim 23, wherein said protein tyrosine kinase is 5 Fgr.
  - 48. The method of claim 23, wherein said protein tyrosine kinase is Src.
- 10 49. The method of claim 23, wherein said protein tyrosine kinase is Yes.
  - 50. The method of claim 23, wherein said protein tyrosine kinase is Blk.

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- 51. The method of claim 23, wherein said protein tyrosine kinase is HER1.
- 52. The method of claim 23, wherein said protein tyrosine kinase is 20 HER2.
  - 53. The method of claim 23, wherein  $R_2$  is other than heteroaryl and  $R_3$  is aryl which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or more groups  $Z_3$ .

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54 The method of claim 23, wherein said compound of the formula III or salt thereof is administered, simultaneously or sequentially, with an antiinflammatory, antiproliferative, chemotherapeutic agent, immunosuppressant, anti-cancer, cytotoxic agent or PTK inhibitor other than a compound of the formula III or salt thereof.

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55. The method of claim 54, wherein said compound of the formula III or salt thereof is administered with one or more of: another PTK inhibitor; cyclosporin A; CTLA4-Ig; antibodies selected from anti-ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, and monoclonal antibody OKT3; agents blocking the interaction between CD40 and gp39; fusion proteins constructed from CD40 and gp39; inhibitors of NF-kappa B function; nonsteroidal antiinflammatory drugs (NSAIDs); steroids; gold compounds; antiproliferative agents; FK506 (tacrolimus, Prograf); mycophenolate mofetil; cytotoxic drugs; TNF-α inhibitors; anti-TNF antibodies or soluble TNF receptor; rapamycin (sirolimus or Rapamune); leflunimide; cyclooxygenase-2 inhibitors; paclitaxel, cisplatin, carboplatin, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, mitomycin C, ecteinascidin 743, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin, etoposide, etoposide phosphate, teniposide, melphalan, vinblastine, vincristine, leurosidine, epothilone, vindesine, leurosine, or derivatives thereof.

- 20 56. A method for the treatment of a T cell mediated disorder, comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 23.
  - 57. The method of claim 56, wherein T cell activation is inhibited.
  - 58. A pharmaceutical composition for the treatment of a protein tyrosine kinase-associated disorder, comprising a pharmaceutically acceptable vehicle or diluent and at least one compound of claim 1.
- 30 59. A compound of formula II or salt thereof:

where

n is 1 or 2

5 X<sub>3</sub> is oxygen or sulur;

A is selected from carbon and nitrogen;

B is selected from nitrogen, oxygen and sulfur

R, is:

(1) hydrogen or R<sub>6</sub>,

where  $R_6$  is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and one or more (preferably, one or two) groups  $Z_3$ ;

- 15 (2)  $-OH \text{ or } -OR_6$ ;
  - (3) -SH or -SR<sub>6</sub>;
  - (4)  $-C(O)_{_{\boldsymbol{q}}}\boldsymbol{H},\,-C(O)_{_{\boldsymbol{q}}}\boldsymbol{R}_{_{\boldsymbol{6}}},\,\text{or}\,-O-C(O)_{_{\boldsymbol{q}}}\boldsymbol{R}_{_{\boldsymbol{6}}},\,\text{where}\,\,\boldsymbol{q}\,\,\text{is}\,\,\boldsymbol{1}\,\,\text{or}\,\,\boldsymbol{2};$
  - (5)  $-SO_3H \text{ or } -S(O)_qR_6;$
  - (6) halo;
- 20 (7) cyano;
  - (8) nitro;
  - $(9) -Z_4-NR_7R_8;$
  - (10)  $-Z_4-N(R_9)-Z_5-NR_{10}R_{11}$ ;
  - (11)  $-Z_4-N(R_{12})-Z_5-R_6;$
- 25 (12) -P(O)(OR<sub>6</sub>)<sub>2</sub>;

R<sub>2</sub> and R<sub>3</sub> are each independently:

- (1) hydrogen or R<sub>s</sub>;
- (2)  $-Z_4-R_6$ ; or

(3)  $-Z_{13}-NR_{7}R_{8}$ ;

 $R_a$  and  $R_s$ :

- (1) are each independently hydrogen or R<sub>s</sub>;
- (2)  $-Z_4-N(R_9)-Z_5-NR_{10}R_{11}$ ;
- 5 (3)  $-N(R_9)Z_4R_6$ ; or
- (4) together with the nitrogen atom to which they are attached complete a 3- to 8-membered saturated or unsaturated heterocyclic ring which is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ , which heterocyclic ring may optionally have fused to it a benzene ring itself unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ;

 $R_{\mbox{\tiny 7}},\,R_{\mbox{\tiny 8}},\,R_{\mbox{\tiny 9}},\,R_{\mbox{\tiny 10}},\,R_{\mbox{\tiny 11}}$  and  $R_{\mbox{\tiny 12}}\!\!:$ 

- (1) are each independently hydrogen or R<sub>s</sub>;
- (2)  $R_7$  and  $R_8$  may together be alkylene, alkenylene or heteroalkyl, completing a 3- to 8-membered saturated or unsaturated ring with the nitrogen atom to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ; or
- (3) any two of  $R_9$ ,  $R_{10}$  and  $R_{11}$  may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ;

 $R_{13}$  is:

- 25 (1) cyano;
  - (2) nitro;
  - (3)  $-NH_2$ ;
  - (4) -NHOalkyl;
  - (5) -OH;
- 30 (6) -NHOaryl;
  - (7) -NHCOOalkyl;

```
(8)
                    -NHCOOaryl;
                    -NHSO2alkyl;
           (9)
           (10)
                    -NHSO, aryl;
           (11)
                    aryl;
 5
           (12)
                    heteroaryl;
           (13)
                    -Oalkyl; or
           (14)
                    -Oaryl;
      R_{14} is:
                    -NO<sub>2</sub>;
           (1)
10
                    -COOalkyl; or
           (2)
           (3)
                    -COOaryl;
      R_{15} is:
           (1)
                    hydrogen;
           (2)
                    alkyl;
15
           (3)
                    aryl;
                     arylalkyl; or
           (4)
           (5)
                    cycloalkyl;
     Z_1, Z_2 and Z_3 are each independently:
                    hydrogen or Z_6, where Z_6 is (i) alkyl, alkenyl, alkynyl,
           (1)
20
                            cycloalkyl, cycloalkylalkyl, cycloalkenyl,
                            cycloalkenylalkyl, aryl, aralkyl, alkylaryl,
                            cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a
                            group (i) which is itself substituted by one or more of
                            the same or different groups (i); or (iii) a group (i) or
                            (ii) which is substituted by one or more of the following
25
                            groups (2) to (16) of the definition of Z_1, Z_2 and Z_3;
           (2)
                    -OH or -OZ,;
                    -SH or -SZ<sub>6</sub>;
           (3)
                    -C(O)_{q}H, -C(O)_{q}Z_{6}, or -O-C(O)_{q}Z_{6};
           (4)
                    -SO_3H, -S(O)_0Z_6; or S(O)_0N(Z_9)Z_6;
30
           (5)
           (6)
                    halo;
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(7) cyano;
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- (8) nitro;
- (9)  $-Z_4-NZ_7Z_8$ ;
- (10)  $-Z_4-N(Z_9)-Z_5-NZ_7Z_8;$
- 5 (11)  $-Z_4-N(Z_{10})-Z_5-Z_6$ ;
  - (12)  $-Z_4-N(Z_{10})-Z_5-H;$
  - (13) oxo;
  - (14)  $-O-C(O)-Z_6$ ;
- any two of Z<sub>1</sub>, Z<sub>2</sub>, and Z<sub>3</sub> may together be alkylene or

  alkenylene completing a 3- to 8-membered saturated

  or unsaturated ring together with the atoms to which
  they are attached; or
- (16) any two of Z<sub>1</sub>, Z<sub>2</sub>, and Z<sub>3</sub> may together be -O-(CH<sub>2</sub>)<sub>r</sub>-O-, where

  r is 1 to 5, completing a 4- to 8-membered ring together

  with the atoms to which they are attached;

 $Z_4$  and  $Z_5$  are each independently:

- (1) a single bond;
- (2)  $-Z_{11}-S(O)_{q}-Z_{12}-;$
- (3)  $-Z_{11}-C(O)-Z_{12}-;$
- 20 (4)  $-Z_{11}$ -C(S)- $Z_{12}$ -;
  - (5)  $-Z_{11}-O-Z_{12}$ ;
  - (6)  $-Z_{11}-S-Z_{12}-;$
  - (7)  $-Z_{11}$ -O-C(O)- $Z_{12}$ -; or
  - (8)  $-Z_{11}-C(O)-O-Z_{12}-;$
- $Z_7, Z_8, Z_9$  and  $Z_{10}$ :
  - (1) are each independently hydrogen or  $Z_6$ ;
- (2)  $Z_7$  and  $Z_8$ , or  $Z_6$  and  $Z_{10}$ , may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with  $Z_1$ ,  $Z_2$  and  $Z_3$ ; or

(3) Z<sub>7</sub> or Z<sub>8</sub>, together with Z<sub>9</sub>, may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with Z<sub>1</sub>, Z<sub>2</sub> and Z<sub>3</sub>;

 $Z_{11}$  and  $Z_{12}$  are each independently:

- (1) a single bond;
- (2) alkylene;
- (3) alkenylene; or
- 10 (4) alkynylene; and

 $Z_{13}$  is:

5

- (1) a single bond;
- (2)  $-Z_{11}-S(O)_{2}-Z_{12}-;$
- (3)  $-Z_{11}-C(O)-Z_{12}-;$
- 15 (4)  $-Z_{11}$ -C(S)- $Z_{12}$ -;
  - (5)  $-Z_{11}-O-Z_{12}-;$
  - (6)  $-Z_{11}-S-Z_{12}-;$
  - (7)  $-Z_{11}$ -O-C(O)- $Z_{12}$ -;
  - (8)  $-Z_{11}$ -C(O)-O- $Z_{12}$ -;
- 20 (9) -C(NR<sub>15</sub>)-;
  - (10)  $-C(CHR_{14})$ -; or
  - (11)  $-C(C(R_{14})_{2})$ -.

providing that said compound is other than

(1) a compound of formula (i)

25

$$R_{2a} \longrightarrow R_{3a} \qquad \qquad R_{5a} \qquad \qquad R_{4a} \qquad \qquad (i)$$

where

R<sub>1a</sub> is alkyl or -C(O)NHNH<sub>2</sub>;

 $R_{2a}$  and  $R_{3a}$  are independently hydrogen, alkyl, -C(O)-(alk); and

 $R_{4a}$  is hydrogen and  $R_{5a}$  is aryl, alkyl-substituted aryl, halosubstituted aryl, aralkyl, cycloalkyl or amino;

Or  $R_{\scriptscriptstyle 4a}$  is alkyl and  $R_{\scriptscriptstyle 5a}$  is alkyl or aryl;

Or  $R_{4a}$  and  $R_{5a}$  together with the nitrogen atom to which they are bonded together from morpholino.

### (2) a compound of formula (vi)

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$$\begin{array}{c|c} R_{4d} & N & CH_3 \\ R_{5d} & N & COOR_{27} \\ \end{array}$$

$$(vi)$$

where

 $R_{\mbox{\tiny 4d}}$  and  $R_{\mbox{\tiny 5d}}$  are independently hydrogen, alkyl, alkenyl, or phenyl;

 $R_{27}$  is hydrogen or alkyl;

# (3) a compound of formula (vii)

$$R_{3e} \xrightarrow[H]{N} R_{55}$$

$$R_{51} \xrightarrow[R_{52}]{R_{53}}$$

$$R_{51} \xrightarrow[R_{52}]{R_{53}}$$

$$(Vii)$$

20 where

 $R_{3e}$  is phenyl, pyridyl or pryimidinyl optionally substituted with halogen or alkyl;

 $R_{\mbox{\tiny 50}}$  and  $R_{\mbox{\tiny 51}}$  are each independently hydrogen, halogen or alkyl;

 $R_{s2}$  and  $R_{s3}$  are each independently hydrogen, halogen, alkyl or haloalkyl;

 $R_{54}$  and  $R_{56}$  are each independently hydrogen, halogen, alkyl, nitro or amino;

 $R_{ss}$  is hydrogen, halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio, or alkoxycarbonyl; and n is zero or 1;

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#### (4) a compound of formula (viii)

where

 $R_{2f}$  and  $R_{3f}$  are independently hydrogen or alkyl

R<sub>s</sub> is hydrogen or alkyl; and

 $R_{\rm sr}$  is alkyl, cycloalkyl, aryl, alkyl-substituted aryl, haloalkyl-substituted aryl, halo-substituted aryl, alkoxy-substituted aryl, nitro-substituted aryl, aryl-substituted aryl, aralkyl, or heteroaryl;

20

or  $R_{\mbox{\tiny sf}}$  and  $R_{\mbox{\tiny sf}}$  together with the nitrogen atom to which they are bonded form a morpholino ring

(5) a compound of formula (ix)

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where

 $R_{2g}$  is H or -N=0;

 $R_{3g}$  is H or alkyl;

 $R_{4g}$  is H or alkyl; and

 $R_{s_g}$  is alkyl, aryl, or aralkyl.

### (6) a compound of formula (x)

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where

 $R_{ih}$  is alkyl or haloalkyl; and

 $R_{\rm 57}$  is alkyl, alkoxy, alkenyl, akenyloxy, alkynyl, alkynyloxy, cycloalkyl, cycloakenyl, cycloalkoxy, cycloalkenyloxy, or phenyl

(7) a compound of formula (xi)

where

R<sub>2i</sub> is hydrogen or alkyl;

 $R_{3i}$  is -C(O)-NH-(alk); and

5  $R_{58}$  and  $R_{59}$  are independently hydrogen, alkyl or halogen.

#### (8) a compound of formula (xii)

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where

 $R_{s_j}$  is alkynyl; and

 $\boldsymbol{R}_{\epsilon_1}$  and  $\boldsymbol{R}_{\epsilon_2}$  are independently alkoxy or haloalkoxy;

### (9) a compound of formula

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## (10) a compound of the formula

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/09753

A. CLASSIFICATION OF SUBJECT MATTER  IPC(6) : A61K 31/426, 31/427, 31/428, 31/438, 31/4709, 31/45, 31/435, 31/4406, 31/4439, 31/496; C07D 277/40, 277/42, 277/46, 277/48, 277/56, 277/62, 295/182, 417/12; A61P 37/06, 19/02, 21/00, 37/02, 35/00, 37/08, 11/06, 27/02  US CL : 544/369; 546/19, 117, 164, 209, 269.7; 548/180, 190, 193, 194, 195, 196; 514/  B. FIELDS SEARCHED				
Minimum documentation searched (classification system followed by classification symbols) U.S.: 544/369; 546/19, 117, 164, 209, 269.7; 548/ 180, 190, 193, 194, 195, 196; 514/				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN Substructure Search				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category *	Citation of document, with indication, where ap	propriate, of the relevant passages	Relevant to claim No.	
X	ALDRICH CHEMICAL COMPANY, 1992 Catalog, page 51, entries 25,301-4 and 28,457-2, page 98 entry A8,980-4.		1-14	
x	US 3,547,917 A (KULKA ET AL) 15 December 1970 (15.12.1970) columns 5-6, Example 9.		1-16 and 23-59	
x	WO 9828282 A2 (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 02 July 1998 page 90 lines 25-32.		1-16 and 23-59	
x	CHUPP, J.P., A novel synthesis of 2,4-thiophenediamines and their behavior as stable reactive enamines, J. Heterocyclic Chem., 1970, Vol. 7, No. 2, pages 285-289, especially compounds 3a and 3b in Scheme 4 on page 287.		1-14 and 59	
x	EREMEEV, A.V. ET AL, Addition of isocyanates and isothiocyanates to 2-amino-3-phenylcarbamoylazirine, Khim. Geterotsikl. Soedin., 1986, No. 2, pages 277-8, especially compound VI in the figure on page 277.		1-7, 10-16 and 23-58	
X	ALI, M.I. ET AL Reactions with naphthoylacetanilides, Egypt. J. Chem., 1979, Vol. 22, No. 3, pages 179-88, especially compound V in the figure on page 180 and in paragraph spanning pages 184-186.  FRY, D.W. Recent advances in Tyrosine Kinase Inhibitors, Annual Reports in Medicinal Chemistry, 1996, Vol 31, pages 151-160.		1-8, 10-15, and 23-59	
A			1-59	
Further documents are listed in the continuation of Box C.  See patent family annex.  See patent family annex.  Later document published after the international filing date or priority				
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specified) cor		considered to involve an inventive significant with one or more other significant.	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
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